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(54) Title: MULTIBINDING AGENTS THAT MODULATE PPARγ AND RXR RECEPTORS

(57) Abstract

Disclosed are novel multi-binding compounds (agents) which bind to PPARγ receptors. The compounds of this invention comprise a plurality of ligands each of which can bind to such receptors thereby modulating the biological processes and/or functions thereof. The ligands are capable of binding to either a PPARγ receptor or a RXR receptor, so long as at least one ligand of the multi-binding compound binds to a PPARγ receptor. Each of the ligands is covalently attached to a linker or linkers which may be the same or different to provide for the multi-binding compound. The linker is selected such that the multi-binding compound so constructed demonstrates increased modulation of the biological processes mediated by the PPARγ receptor.

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MULTIBINDING AGENTS THAT MODULATE PPARγ AND RXR RECEPTORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of United States Provisional Serial Number 60/088,466, filed June 8, 1998, and United States Provisional Serial Number 60/092,938, filed July 15, 1998.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to novel therapeutic agents which bind to mammalian receptors and modulate their activity. More particularly, the invention relates to novel therapeutic agents that bind to and modulate the *in vivo* activity of PPARγ and RXR receptors in mammals by acting as multi-binding compounds. The therapeutic agents or multi-binding compounds described herein comprise at least two ligands connected by a linker or linkers, wherein said ligands in their monovalent state bind to and/or are capable of modulating the activity of the PPARγ and RXR receptors. The linking moiety is chosen such that the multi-binding compounds so constructed demonstrate increased biological activity as compared to the same number of individual units of the ligand or ligands. The invention also relates to methods of using such compounds, to methods of preparing such compounds and to pharmaceutical compositions containing them.

These multi-binding compounds are particularly useful in treating mammalian conditions that are mediated by the PPARγ receptors targeted by the ligands, such as non-insulin dependent diabetes mellitus, cancer, including colon carcinomas and lipocarcinomas, hyperlipidemia, atherosclerosis and inflammatory

diseases such as rheumatoid arthritis and inflammatory bowel disease. Accordingly, this invention also relates to pharmaceutical compositions comprising a pharmaceutically acceptable excipient and an effective amount of a multi-binding compound of this invention.

Publications cited herein are incorporated by reference in their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference in its entirety.

State of the Art

A receptor is a biological structure with one or more binding domains that reversibly complexes with one or more ligands, where that complexation has biological consequences.

Receptors can exist entirely outside the cell (extracellular receptors), within the cell membrane (but presenting sections of the receptor to the extracellular milieu and cytosol), or entirely within the cell (intracellular receptors). They may also function independently of a cell (e.g., clot formation). Receptors within the cell membrane allow a cell to communicate with the space outside of its boundaries (i.e., signaling) as well as to function in the transport of molecules and ions into and out of the cell.

A ligand is a binding partner for a specific receptor or family of receptors. A ligand may be the endogenous ligand for the receptor or alternatively may be a synthetic ligand for the receptor such as a drug, a drug candidate or a pharmacological tool.

The ligands that bind to cellular receptors may be specifically classified as follows:

1. Full agonists - ligands that when bound trigger the maximum activity seen by natural ligands;

2. Partial agonists- ligands that when bound trigger sub-maximal activity;

3. Antagonist- ligands that when bound inhibit or prevent the activity arising from a natural ligand binding to the receptor. Antagonists may be of the surmountable class (results in the parallel displacement of the dose-response curve of the agonist to the right in a dose dependent fashion without reducing the maximal response for the agonist) or insurmountable class (results in depression of the maximal response for a given agonist with or without the parallel shift);

4. Inverse antagonist-ligands that when bound decrease the basal activity of the unbound receptor (if any).

There are four fundamental measurable properties that pertain to the interaction of a ligand with its receptor:

1) the affinity of the ligand for the receptor, which relates to the energetics of the binding;

2) the efficacy of the ligand for the receptor, which relates to the functional downstream activity of the ligand;

3) the kinetics of the ligand for the receptor, which defines the onset of action and the duration of action; and

4) the desensitization of the receptor for the ligand.

With regard to the ligand, it is the combination of these properties that provides the foundation for defining the nature of the functional response. Thus, an activating ligand (or agonist) has affinity for the receptor and downstream efficacy. In contrast, an inhibiting ligand (antagonist) has affinity for the receptor but no efficacy.

Selectivity defines the ratios of affinities or the ratios of efficacies of a given ligand compared across two receptors. It is the selectivity of a specific drug that provides the required biological profile.

Current drugs (ligands) targeting PPARγ receptors have clinical shortcomings identified by one or more of low efficacy, low affinity, poor safety profile, lack of selectivity or overselectivity for the intended receptor, and suboptimal duration of action and onset of action. Accordingly, it would be beneficial to develop ligands that have improved affinity, efficacy, selectivity, onset of action and duration of action.

Affinity of ligand for target receptor

An increase in ligand affinity to the target receptor may contribute to reducing the dose of ligand required to induce the desired therapeutic effect. A reduction in ligand affinity will remove activity and may contribute to the selectivity profile for a ligand.

Efficacy of ligand at a target receptor (functional effect)

An increased ligand efficacy at a target receptor can lead to a reduction in the dose required to mediate the desired therapeutic effect. This increase in efficacy may arise from an improved positive functional response of the ligand or a change from a partial to full agonist profile. Reduced efficacy of a full agonist to a partial agonist may provide clinical benefit by modulating the biological response.

Selectivity of ligand compared across receptor subtypes

An increase in the selectivity of the ligand across receptor subtypes requires that the affinity or efficacy of the ligand at other receptors is reduced relative to the desired receptor.

Onset of Action

More rapid onset of action of the ligand to effect a biological response is often preferred.

Duration of Action

An increased duration of action of the ligand to effect a biological response may be preferred. For example β_2 adrenergic agonists such as albuterol have a relatively short duration of action of approximately 3-4 hours and an increase in duration of action would simplify the dosing regimen required to administer this drug (ligand).

The nuclear receptor superfamily comprises a number of ligand-activated transcription factors which control a wide range of biological processes involving gene expression such as differentiation, development and homeostasis. This superfamily of receptors includes the estrogen (ER), thyroid(TR), progesterone (PR) and retinoid receptors (RXR, RAR), in addition to the peroxisome proliferator-activated receptors (PPARα, PPARδ, and PPARγ). These receptors possess the common structural motifs of an amino-terminal ligand independent transactivation domain, a central DNA binding domain, and a carboxy-terminal ligand-binding domain (LBD). The central DNA binding domain recognizes a specific sequence of DNA, termed generically the Hormone Response Element (HRE). Activation of these receptors is associated with the binding of specific small molecule ligands to the LBD site, which then correlates with the association of the DNA binding domain with an HRE site on DNA, leading to transcriptional events. There is a body of crystallographic and biological evidence indicating that this class of receptors functions as a homo- or hetero-dimeric complex. For a review, see **Cell** Vol 83 (1995) 835-839.

The peroxisome proliferator-activated receptor gamma (PPARγ) is found principally in adipocytes and forms a functional heterodimer with the retinoid X receptor (RXR). Receptor dimerization has been shown to be required for functional gene expression via activation of the nuclear receptors. Activation of the PPARγ-RXR heterodimer by PPARγ-specific or RXR-specific ligands in preadipocytes promotes gene transcription and differentiation to adipocytes. Thus, either ligand can activate the heterodimeric receptor complex. Administration of PPARγ ligands or RXR ligands to mammals with hyperglycemia, hyperinsulinemia, or hypertriglyceridemia leads to a reduction of blood glucose, serum triglycerides and serum non-esterified fatty acids, in addition to the differentiation of adipocytes. Additionally, the co-administration of a PPARγ ligand and an RXR ligand to cells over-expressing the PPARγ-RXR heterodimer is synergistic in activating gene transcription. The coadministration of a PPARγ ligand and an RXR ligand to a hyperglycemic mammal leads to an enhancement of the glucose- and lipid-lowering effects compared to administration of either ligand alone. See Nature Vol 386 (1197) 407-410 and Mol. and Cell Biol. Vol 18 (1998) 3483-3494.

Accordingly, novel ligands having desired potency and therapeutic effect for the PPARγ receptor would be particularly desirable in order to further increase insulin sensitivity, especially in the case of non-insulin dependent diabetes mellitus (NIDDM) in mammalian patients. Such novel ligands would preferably achieve the desired potency and therapeutic effect by modulating one or more of the ligand's properties as to efficacy, affinity, safety profile, selectivity, duration of action and/or onset of action. This may have advantages in the effects on other disease states as well, such as certain types of cancer, hyperlipidemia, atherosclerosis and inflammatory diseases.

SUMMARY OF THE INVENTION

This invention is directed to general synthetic methods for generating large libraries of diverse multimeric compounds which multimeric compounds are candidates for possessing multibinding properties. The diverse multimeric compound libraries provided by this invention are synthesized by combining a linker or linkers with a ligand or ligands to provide for a library of multimeric compounds wherein the linker and ligand each have complementary functional groups permitting covalent linkage. The library of linkers is preferably selected to have diverse properties such as valency, linker length, linker geometry and rigidity, hydrophilicity or hydrophobicity, amphiphilicity, acidity, basicity and polarization. The library of ligands is preferably selected to have diverse attachment points on the same ligand, different functional groups at the same site of otherwise the same ligand, and the like.

This invention is also directed to libraries of diverse multimeric compounds which multimeric compounds are candidates for possessing multibinding properties. These libraries are prepared via the methods described above and permit the rapid and efficient evaluation of what molecular constraints impart multibinding properties to a ligand or a class of ligands targeting a receptor.

Accordingly, in one of its composition aspects, this invention is directed to a multi-binding compound and salts thereof comprising 2 to 10 ligands, which may be the same or different and which are covalently attached to a linker or linkers which may be the same of different, at least one of said ligands comprising a ligand domain capable of binding to a PPARγ receptor, and a second ligand being capable of binding to an RXR receptor. Preferably, at least two and more preferably each of the ligands comprises a ligand domain capable of binding to one or more of a PPARγ receptor or a RXR receptor.

The multi-binding compounds of this invention are preferably represented by formula I:

$$(L)_p(X)_q \qquad I$$

wherein each L is independently selected from ligands comprising a ligand domain capable of binding to one or more of a PPARγ receptor or a RXR receptor; X is independently a linker; p is an integer of from 2 to 10; q is an integer of from 1 to 20; and pharmaceutically acceptable salts thereof, with the proviso that where one ligand binds to an RXR receptor, at least one other ligand binds to a PPARγ receptor. Preferably, q is less than p.

In another of its composition aspects, this invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and an effective amount of a multi-binding compound, or a pharmaceutically acceptable salt thereof, comprising 2 to 10 ligands which may be the same or different and which are covalently attached to a linker or linkers which may be the same or different, at least one of said ligands comprising a ligand domain capable of binding to one or more of a PPARγ receptor or a RXR receptor, with the proviso that where one ligand binds to an RXR receptor, at least one other ligand binds to a PPARγ receptor.

Preferably, said ligands comprising a ligand domain capable of binding to one or more of a PPARγ receptor or RXR receptor modulate insulin sensitivity in mammals. More preferably, said ligands are selected from the group selected from Formulas A-K and II-IV presented herein. In all embodiments, at least one ligand is a PPARγ ligand.

In still another of its composition aspects, this invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and an effective amount of a multi-binding compound represented by formula I:

$$(L)_p(X)_q \qquad I$$

wherein each L is independently selected from ligands comprising a ligand domain capable of binding to a PPARγ receptor or RXR receptor; X is a linker; *p* is an integer of from 2 to 10; *q* is an integer of from 1 to 20; and pharmaceutically acceptable salts thereof, with the proviso that where one ligand binds to an RXR receptor, at least one other ligand binds to a PPARγ receptor. Preferably, *q* is less than *p*, and more preferably the ligand is selected from the group represented by Formulas A-K and II-IV herein.

In one of its method aspects, this invention is directed to a method for increasing insulin sensitivity in a mammal mediated by one or more of PPARγ and RXR receptors, which method comprises administering to said mammal an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a multi-binding compound, or a pharmaceutically acceptable salt thereof, comprising 2 to 10 ligands which may be the same or different and which are covalently attached to a linker or linkers which may be the same or different, at least two of said ligands comprising a ligand domain capable of binding to one or more of PPARγ and RXR receptors, with the proviso that at least one ligand is a PPARγ ligand.

In another of its method aspects, this invention is directed to a method for treating diseases including NIDDM, cancer, hyperlipidimia, atherosclerosis and inflammatory diseases, especially NIDDM, in a mammal mediated by PPARγ receptors which method comprises administering to said mammal an effective

amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a multi-binding compound represented by formula I:

$$(L)_p(X)_q \qquad I$$

wherein each L is independently selected from ligands comprising a ligand domain capable of binding to at least one of a PPARγ or RXR receptor mediating insulin sensitivity; X is a linker; *p* is an integer of from 2 to 10; *q* is an integer of from 1 to 20 and pharmaceutically acceptable salts thereof, wherein at least one ligand must bind to the PPARγ receptor.

Preferably, *q* is less than *p*, and more preferably, the ligand is selected from the group consisting of PPARγ and RXR ligands as set forth in Formulas A-K and II-IV herein. However, in one embodiment, at least one of the ligands in said multi-binding compound is a corticosteroid.

Accordingly, in one of its method aspects, this invention is directed to a method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in (c) above to identify multimeric ligand compounds possessing multibinding properties.

In another of its method aspects, this invention is directed to a method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in (c) above to identify multimeric ligand compounds possessing multibinding properties.

The preparation of the multimeric ligand compound library is achieved by either the sequential or concurrent combination of the two or more stoichiometric equivalents of the ligands identified in (a) with the linkers identified in (b). Sequential addition is preferred when a mixture of different ligands is employed to ensure heterodimeric or multimeric compounds are prepared. Concurrent addition of the ligands is preferred when at least a portion of the multimeric compounds prepared are homomultimeric compounds.

The assay protocols recited in (d) can be conducted on the multimeric ligand compound library produced in (c) above, or preferably, each member of the library is isolated by preparative liquid chromatography mass spectrometry (LCMS).

In one of its composition aspects, this invention is directed to a library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

In another of its composition aspects, this invention is directed to a library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

In a preferred embodiment, the library of linkers employed in either the methods or the library aspects of this invention is selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers. For example, in one embodiment, each of the linkers in the linker library may comprise linkers of different chain length and/or having different complementary reactive groups. Such linker lengths can preferably range from about 2 to 100Å.

In another preferred embodiment, the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands in order to provide for a range of orientations of said ligand on said multimeric ligand compounds. Such reactive functionality includes, by way of example, carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates and precursors thereof. It is understood, of course, that the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

In other embodiments, the multimeric ligand compound is homomeric (i.e., each of the ligands is the same PPARγ ligand, although it may be attached at different points) or heteromeric (i.e., at least one of the ligands is different from the other ligands).

In addition to the combinatorial methods described herein, this invention provides for an iterative process for rationally evaluating what molecular constraints impart multibinding properties to a class of multimeric compounds or ligands targeting a receptor. Specifically, this method aspect is directed to a

method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

(a) preparing a first collection or iteration of multimeric compounds which is prepared by contacting at least two stoichiometric equivalents of the ligand or mixture of ligands which target a receptor with a linker or mixture of linkers wherein said ligand or mixture of ligands comprises at least one reactive functionality and said linker or mixture of linkers comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand wherein said contacting is conducted under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands;

(b) assaying said first collection or iteration of multimeric compounds to assess which if any of said multimeric compounds possess multibinding properties;

(c) repeating the process of (a) and (b) above until at least one multimeric compound is found to possess multibinding properties;

(d) evaluating what molecular constraints imparted multibinding properties to the multimeric compound or compounds found in the first iteration recited in (a)- (c) above;

(e) creating a second collection or iteration of multimeric compounds which elaborates upon the particular molecular constraints imparting multibinding properties to the multimeric compound or compounds found in said first iteration;

(f) evaluating what molecular constraints imparted enhanced multibinding properties to the multimeric compound or compounds found in the second collection or iteration recited in (e) above;

(g) optionally repeating steps (e) and (f) to further elaborate upon said molecular constraints.

Preferably, steps (e) and (f) are repeated at least two times, more preferably at least from 2-50 times, even more preferably from at least 3 to 50 times, and still more preferably at least 5-50 times.

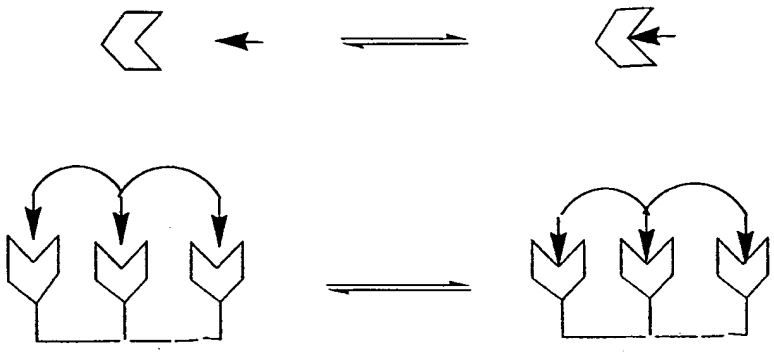
DETAILED DESCRIPTION OF THE INVENTION

Ligand (drug) interactions with cellular receptors are controlled by molecular interaction/recognition between the ligand and the receptor. In turn, such interaction can result in modulation or disruption of the biological processes/functions of these receptors and, in some cases, leads to cell death. Accordingly, when cellular receptors mediate mammalian pathologic conditions, interactions of the ligand with the cellular receptor can be used to treat these conditions. Of particular interest are mammalian PPARγ and RXR receptors which are known to affect insulin sensitivity, serum triglyceride levels and free fatty acids, as well as other important functions controlled by gene expression. As noted above, this invention is directed, in part, to multi-binding compounds that bind PPARγ and RXR receptors.

The "affinity" and "specificity" of the PPARγ and RXR receptors and ligands thereto are dependent upon the complementarity of molecular binding surfaces and the energetic costs of complexation. "Affinity" is sometimes quantified by the equilibrium constant of complex formation. Specificity relates to the difference in affinity between the same ligand binding to different ligand binding sites on the cellular receptor.

The multi-binding compounds of this invention are capable of acting as multi-binding agents and the surprising activity of these compounds arises at least in part from their ability to bind in a multivalent manner with mammalian PPARγ and optionally RXR receptors. Multivalent binding interactions are characterized by the concurrent interaction of multiple ligands with multiple ligand binding sites

on one or more PPARγ and optionally RXR receptors. Multivalent interactions differ from collections of individual monovalent interactions by imparting enhanced biological and/or therapeutic effect. Examples of multivalent binding interactions (e.g., trivalent) relative to monovalent binding interactions are shown below:



Just as multivalent binding can amplify binding affinities, it can also amplify differences in binding affinities, resulting in enhanced binding specificity as well as affinity.

Definitions:

Prior to discussing this invention in further detail, the following terms will first be defined.

The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms, and even more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, *n*-decyl, tetradecyl, and the like.

The term "substituted alkyl" refers to an alkyl group as defined above, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted

cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl and -SO_2-heteroaryl.

The term "alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms and even more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methylene (-CH_2-), ethylene (-CH_2CH_2-), the propylene isomers (e.g., -$CH_2CH_2CH_2$- and -$CH(CH_3)CH_2$-) and the like.

The term "substituted alkylene" refers to an alkylene group, as defined above, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl and -SO_2-heteroaryl. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl

groups fused to the alkylene group. Preferably such fused groups contain from 1 to 3 fused ring structures.

The term "alkaryl" refers to the groups -alkylene-aryl and -substituted alkylene-aryl where alkylene, substituted alkylene and aryl are defined herein. Such alkaryl groups are exemplified by benzyl, phenethyl and the like.

The term "alkoxy" refers to the groups alkyl-O-, alkenyl-O-, cycloalkyl-O-, cycloalkenyl-O-, and alkynyl-O-, where alkyl, alkenyl, cycloalkyl, cycloalkenyl, and alkynyl are as defined herein. Preferred alkoxy groups are alkyl-O- and include, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

The term "substituted alkoxy" refers to the groups substituted alkyl-O-, substituted alkenyl-O-, substituted cycloalkyl-O-, substituted cycloalkenyl-O-, and substituted alkynyl-O- where substituted alkyl, substituted alkenyl, substituted cycloalkyl, substituted cycloalkenyl and substituted alkynyl are as defined herein.

The term "alkylalkoxy" refers to the groups -alkylene-O-alkyl, -alkylene-O-substituted alkyl, -substituted alkylene-O-alkyl and -substituted alkylene-O-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylalkoxy groups are alkylene-O-alkyl and include, by way of example, methylenemethoxy ($-CH_2OCH_3$), ethylenemethoxy ($-CH_2CH_2OCH_3$), *n*-propylene-*iso*-propoxy ($-CH_2CH_2CH_2OCH(CH_3)_2$), methylene-*t*-butoxy ($-CH_2-O-C(CH_3)_3$) and the like.

The term "alkylthioalkoxy" refers to the group -alkylene-S-alkyl,

alkylene-S-substituted alkyl, substituted alkylene-S-alkyl and substituted alkylene-S-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylthioalkoxy groups are alkylene-S-alkyl and include, by way of example, methylenethiomethoxy ($-CH_2SCH_3$), ethylenethiomethoxy ($-CH_2CH_2SCH_3$), *n*-propylene-*iso*-thiopropoxy ($-CH_2CH_2CH_2SCH(CH_3)_2$), methylene-*t*-thiobutoxy ($-CH_2SC(CH_3)_3$) and the like.

The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. Preferred alkenyl groups include ethenyl ($-CH=CH_2$), *n*-propenyl ($-CH_2CH=CH_2$), *iso*-propenyl ($-C(CH_3)=CH_2$), and the like.

The term "substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "alkenylene" refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and

having at least 1 and preferably from 1-6 sites of vinyl unsaturation. This term is exemplified by groups such as ethenylene (-CH=CH-), the propenylene isomers (e.g., $-CH_2CH=CH-$ and $-C(CH_3)=CH-$) and the like.

The term "substituted alkenylene" refers to an alkenylene group as defined above having from 1 to 5 substituents, and preferably from 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl. Additionally, such substituted alkenylene groups include those where 2 substituents on the alkenylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkenylene group.

The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 20 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynyl groups include ethynyl ($-C\equiv CH_2$), propargyl ($-CH_2C\equiv CH$) and the like.

The term "substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy,

amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "alkynylene" refers to a diradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynylene groups include ethynylene (-C≡C-), propargylene (-CHC≡C-) and the like.

The term "substituted alkynylene" refers to an alkynylene group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "acyl" refers to the groups HC(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, cycloalkenyl-C(O)-, substituted cycloalkenyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)- where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl,

cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "acylamino" refers to the group -C(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic or where both R groups are joined to form a heterocyclic group (e.g., morpholino) wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "aminoacyl" refers to the group -NRC(O)R where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "aminoacyloxy" refers to the group -NRC(O)OR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, aryl-C(O)O-, heteroaryl-C(O)O-, and heterocyclic-C(O)O- wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like.

Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

The term "aryloxy" refers to the group aryl-O- wherein the aryl group is as defined above including optionally substituted aryl groups as also defined above.

The term "arylene" refers to the diradical derived from aryl (including substituted aryl) as defined above and is exemplified by 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,2-naphthylene and the like.

The term "amino" refers to the group $-NH_2$.

The term "substituted amino" refers to the group -NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic provided that both R's are not hydrogen.

The term "carboxyalkyl" refers to the groups "-C(O)O-alkyl", "-C(O)O-substituted alkyl", "-C(O)O-cycloalkyl", "-C(O)O-substituted cycloalkyl", "-C(O)O-alkenyl", "-C(O)O-substituted alkenyl", "-C(O)O-alkynyl" and "-C(O)O-substituted alkynyl" where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl are as defined herein.

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

The term "substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 20 carbon atoms having a single cyclic ring and at least one point of internal unsaturation. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl and the like.

The term "substituted cycloalkenyl" refers to cycloalkenyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

The term "heteroaryl" refers to an aromatic group of from 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring).

Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl,

and thioalkoxy. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

The term "heteroaryloxy" refers to the group heteroaryl-O-.

The term "heteroarylene" refers to the diradical group derived from heteroaryl (including substituted heteroaryl), as defined above, and is exemplified by the groups 2,6-pyridylene, 2,4-pyridiylene, 1,2-quinolinylene, 1,8-quinolinylene, 1,4-benzofuranylene, 2,5-pyridnylene, 2,5-indolenyl and the like.

The term "heterocycle" or "heterocyclic" refers to a monoradical saturated unsaturated group having a single ring or multiple condensed rings, from 1 to 40 carbon atoms and from 1 to 10 hetero atoms, preferably 1 to 4 heteroatoms, selected from nitrogen, sulfur, phosphorus, and/or oxygen within the ring.

Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic groups can be optionally substituted with 1 to 5, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl. Such heterocyclic groups can have a single ring or multiple condensed rings. Preferred heterocyclics include morpholino, piperidinyl, and the like.

Examples of nitrogen heterocycles and heteroaryls include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, morpholino, piperidinyl, tetrahydrofuranyl, and the like as well as N-alkoxy-nitrogen containing heterocycles.

A preferred class of heterocyclics include "crown compounds" which refers to a specific class of heterocyclic compounds having one or more repeating units of the formula $[-(CH_2-)_mY-]$ where *m* is ≥ 2, and Y at each separate occurrence can be O, N, S or P. Examples of crown compounds include, by way of example only, $[-(CH_2)_3-NH-]_3$, $[-((CH_2)_2-O)_4-((CH_2)_2-NH)_2]$ and the like. Typically such crown compounds can have from 4 to 10 heteroatoms and 8 to 40 carbon atoms.

The term "heterocyclooxy" refers to the group heterocyclic-O-.

The term "thioheterocyclooxy" refers to the group heterocyclic-S-.

The term "heterocyclene" refers to the diradical group formed from a heterocycle, as defined herein, and is exemplified by the groups 2,6-morpholino, 2,5-morpholino and the like.

The term "oxyacylamino" refers to the group -OC(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic

wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "pseudohalide" refers to functional groups which react in displacement reactions in a manner similar to a halogen. Such functional groups include, by way of example, mesyl, tosyl, azido and cyano groups.

The term "thiol" refers to the group -SH.

The term "thioalkoxy" refers to the group -S-alkyl.

The term "substituted thioalkoxy" refers to the group -S-substituted alkyl.

The term "thioaryloxy" refers to the group aryl-S- wherein the aryl group is as defined above including optionally substituted aryl groups also defined above.

The term "thioheteroaryloxy" refers to the group heteroaryl-S- wherein the heteroaryl group is as defined above including optionally substituted aryl groups as also defined above.

As to any of the above groups which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds.

The term "pharmaceutically acceptable salt" refers to salts which retain the biological effectiveness and properties of the multi-binding compounds of this invention and which are not biologically or otherwise undesirable. In many cases,

the multi-binding compounds of this invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted cycloalkyl amines, disubstituted cycloalkyl amine, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amine, trisubstituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group.

Examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(*iso*-propyl) amine, tri(*n*-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine,

arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example, carboxylic acid amides, including carboxamides, lower alkyl carboxamides, dialkyl carboxamides, and the like.

Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluene-sulfonic acid, salicylic acid, and the like.

The term "protecting group" or "blocking group" refers to any group which when bound to one or more hydroxyl, thiol, amino or carboxyl groups of the compounds (including intermediates thereof) prevents reactions from occurring at these groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl, thiol, amino or carboxyl group (Green, *Protective Groups in Organic Synthesis*, 2nd Ed., John Wiley & Sons, NY, NY (1991)). The particular removable blocking group employed is not critical and preferred removable hydroxyl blocking groups include conventional substituents such as allyl, benzyl, acetyl, chloroacetyl, thiobenzyl, benzylidine, phenacyl, t-butyl-diphenylsilyl and any other group that can be introduced chemically onto a hydroxyl functionality and later selectively removed either by chemical or enzymatic methods in mild conditions compatible with the nature of the product.

Preferred removable amino blocking groups include conventional substituents such as t-butyoxycarbonyl (t-BOC), benzyloxycarbonyl (CBZ), and the like which can be removed by conventional conditions compatible with the nature of the product.

Preferred carboxyl protecting groups include esters such as methyl, ethyl, propyl, *t*-butyl etc. which can be removed by mild hydrolysis conditions compatible with the nature of the product.

The term "optional" or "optionally" means that the subsequently described event, circumstance or substituent may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

As used herein, the terms "inert organic solvent" or "inert solvent" mean a solvent inert under the conditions of the reaction being described in conjunction therewith [including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform ($CHCl_3$), methylene chloride (or dichloromethane or "CH_2Cl_2"), diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, tert-butanol, dioxane, pyridine, and the like]. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

The "PPARγ receptor" is a receptor and plays a role in the mechanisms of insulin sensitivity. PPARγ receptors are located primarily in adipose tissues throughout the body. The PPARγ receptor forms a heterodimer with the RXR receptor. Together, they act to affect insulin sensitivity in the cell, particularly as results from NIDDM, and may affect inflammatory diseases such as rheumatoid

arthritis and inflammatory bowel disease, cancer such as colon carcinoma and lipocarcinoma, hyperlipidemia and arterioclerosis.

It should be recognized that the PPARγ and RXR receptors that participate in biological multivalent binding interactions are constrained to varying degrees by their intra- and intermolecular associations (e.g. cellular receptors may be covalently joined in a single structure, noncovalently associated in a multimeric structure, embedded in a membrane or polymeric matrix and so on) and therefore have less translational and rotational freedom than if the same cellular receptors were present as monomers in solution.

The term "library" refers to at least 3, preferably from 10^2 to 10^9 and more preferably from 10^2 to 10^4 multimeric compounds. Preferably, these compounds are prepared as a multiplicity of compounds in a single solution or reaction mixture which permits facile synthesis thereof. In one embodiment, the library of multimeric compounds can be directly assayed for multibinding properties. In another embodiment, each member of the library of multimeric compounds is first isolated and, optionally, characterized. This member is then assayed for multibinding properties.

The term "collection" refers to a set of multimeric compounds which are prepared either sequentially or concurrently (e.g., combinatorially). The collection comprises at least 2 members; preferably from 2 to 10^9 members and still more preferably from 10 to 10^4 members.

The term "ligand binding site" as used herein denotes the site on the PPARγ or RXR receptor that recognizes a ligand domain and provides a binding partner for that ligand. The ligand binding site may be defined by monomeric or multimeric structures. This interaction may be capable of producing a unique

biological effect, for example agonism, antagonism, modulatory effect and the like or may maintain an ongoing biological event.

"PPARγ Ligand" as used herein denotes a compound that is a binding partner for the PPARγ receptor and is bound thereto by complementarity. The specific region or regions of the ligand that is (are) recognized by the PPARγ receptor is designated as the "PPAR ligand domain". A ligand may be either capable of binding to a receptor by itself, or may require the presence of one or more non-ligand components for binding (e.g., Ca^{+2}, Mg^{+2} or a water molecule).

"RXR Ligand" as used herein denotes a compound that is a binding partner for the RXR receptor and is bound thereto by complementarity. The specific region or regions of the ligand that is (are) recognized by the RXR receptor is designated as the "RXR ligand domain". A ligand may be either capable of binding to a receptor by itself, or may require the presence of one or more non-ligand components for binding (e.g., Ca^{+2}, Mg^{+2} or a water molecule).

It is further understood that the term "PPARγ ligand" or "RXR ligand" is not intended to be limited to compounds known to be useful as PPARγ and RXR receptor binding compounds (e.g., known drugs). It should also be understood that portions of the ligand structure that are not essential for specific molecular recognition and binding activity may be varied substantially, replaced with unrelated structures and, in some cases, omitted entirely without affecting the binding interaction. The primary requirement for the ligand is that it has a ligand domain as defined above. Those skilled in the art will understand that the term ligand can equally apply to a molecule that is not normally associated with PPARγ and RXR cellular receptor binding properties. In addition, it should be noted that ligands that exhibit marginal activity or lack useful activity as monomers can be

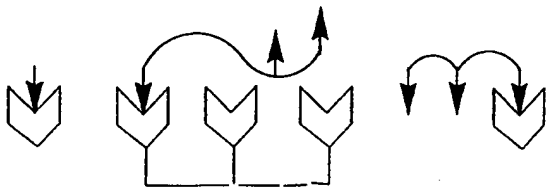
highly active as multivalent compounds because of the benefits conferred by multivalency. The only requirement for a ligand is that it has a ligand binding domain as defined above.

A "multimeric compound" refers to a compound that is capable of multivalency as defined below, and which has 2 to 10 ligands covalently bound to one or more linkers which may be the same or different. The compound may or may not possess multibinding properties. At least one of the ligands comprises a ligand domain capable of binding to one or more PPARγ receptors, and optionally RXR receptors. The multi-binding compound provides a biological and/or therapeutic effect greater than the aggregate of unlinked ligands equivalent thereto which may be the same or different which unlinked ligands comprise a ligand domain capable of binding to one or more PPARγ receptors, and optionally RXR receptors. That is to say that the biological and/or therapeutic effect of the PPARγ and/or RXR binding ligands attached to the multi-binding compound is greater than that achieved by the same amount of unlinked PPARγ and/ or RXR ligands made available for binding to the ligand binding sites.

The phrase "increased biological or therapeutic effect" includes, for example increased affinity for a target, increased specificity for a target, increased selectivity for a target, increased potency, increased efficacy, decreased toxicity, improved duration of action, decreased side effects, increased therapeutic index, improved bioavailability, improved pharmacokinetics, improved activity spectrum, and the like. The multi-binding compounds of this invention will exhibit at least one and preferably more than one of the above mentioned effects.

"Uni-valency" as used herein refers to a single binding interaction between one ligand as defined herein with one ligand binding site as defined herein. It should be noted that a molecule having multiple copies of a ligand (or ligands)

exhibits uni-valency when only one ligand is interacting with a ligand binding site. Examples of a univalent interaction are depicted below.



"Multi-valency" as used herein refers to the concurrent binding of from 2 to 10 linked ligands (which may be the same or different) and two or more corresponding ligand binding sites on the receptors which receptors may be the same or different.

For example, two ligands connected by a linker that bind concurrently to two ligand binding sites would be considered as bi-valency; three ligands thus connected would be an example of tri-valency. An example of tri-valency illustrating a multi-binding agent bearing three ligands versus a monovalent binding interaction is shown below:

univalent interaction

trivalent interaction

It should be understood that all compounds that contain multiple copies of a ligand attached to a linker do not necessarily exhibit the phenomena of multi-valency, i.e., that the biological and/or therapeutic effect of the multi-binding agent is greater than the sum of the aggregate of unlinked ligands made available to the ligand binding site. For multivalency to occur, the ligands that are connected by a linker have to be presented to their receptors by the linker in a specific manner in order to bring about the desired ligand-orienting result, and thus produce a multi-binding agent.

"Potency" as used herein refers to the minimum concentration at which a ligand is able to achieve a desirable biological or therapeutic effect. The potency of a ligand is typically proportional to its affinity for its ligand binding site. In some cases the potency may be non-linearly correlated with its affinity. In comparing the potency of two drugs, e.g., a multi-binding agent and the aggregate of its unlinked ligand, the dose-response curve of each is determined under identical test conditions (e.g. an *in vitro* or *in vivo* assay, in an appropriate animal model such as a human patient). The finding that the multi-binding agent produces an equivalent biological or therapeutic effect at a lower concentration than the aggregate unlinked ligand (e.g. on a per weight, per mole or per ligand basis) is indicative of enhanced potency.

"Selectivity" or "specificity" is a measure of the binding preferences of a ligand for different ligand binding sites. The selectivity of a ligand with respect to its target ligand binding site relative to another ligand binding site is given by the ratio of the respective values of K_d (i.e., the dissociation constants for each ligand-receptor complex) or in cases where a biological effect is observed below the K_d, the ratio of the respective EC_{50} s (i.e., the concentrations that produce 50% of the maximum response for the ligand interacting with the two distinct ligand binding sites).

The terms "agonism" and "antagonism" are well known in the art. The term "modulatory effect" refers to the ability of the ligand to change the activity of an agonist or antagonist through binding to a ligand binding site.

The term "partial agonist" refers to a receptor agonist which cannot fully elicit a maximal response when it binds to the receptor, no matter how high the concentration of the partial agonist. A partial agonist is able to combine with the receptor, but the full effect of the binding is not elicited. This term is well known in the art and a discussion of it may be found in Textbook of Receptor Pharmacology, ch 1.4, J. Foreman and T. Johansen eds., CRC Press, 1996.

The term "treatment" refers to the treatment of diabetes, in particular insulin sensitivity in a mammal, particularly a human, and includes:

(i) increasing insulin sensitivity in a subject;

(ii) lowering insulin, triglyceride and free fatty acid serum levels; or

(iii) relieving or reducing insulin resistance, e.g., relieving or reducing the intensity and/or severity of the insulin resistance.

The term "therapeutically effective amount" refers to that amount of multi-binding compound which is sufficient to effect treatment, as defined above, when administered to a mammal in need of such treatment. The therapeutically effective amount will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

The term "linker," identified where appropriate by the symbol "X", refers to a group or groups that covalently link(s) from 2 to 10 ligands (as identified above) in a manner that provides for a compound capable of multi-valency when in

the presence of at least one cellular receptor having 2 or more ligand binding sites. The linker is a ligand-orienting entity which may be chiral or achiral that permits attachment of multiple copies of a ligand (which may be the same or different) thereto. In some cases the linker may be biologically active. The term linker does not, however, extend to cover solid inert supports such as beads, glass particles, fibers and the like. But it is to be understood that the multi-binding compounds of this invention can be attached to a solid support if desired, for example, for use in separation and purification processes and for similar applications.

The ligands and linkers which comprise the multibinding agents of the invention and the multibinding compounds themselves may have various stereoisomeric forms, including enantiomers and diastereomers. It is to be understood that the invention contemplates all possible stereoisomeric forms of multibinding compounds, and mixtures thereof.

The extent to which multivalent binding is realized depends upon the efficiency with which the linker or linkers that joins the ligands presents them to their ligand binding sites on one or more receptors. Beyond presenting ligands for multivalent interactions with ligand binding sites, the linker spatially constrains these interactions to occur within dimensions defined by the linker. Thus the structural features of the linker (valency, geometry, orientation, size, flexibility, chemical composition) are features of multivalent compounds that play an important role in determining their activities.

Methodology

The linker, when covalently attached to the ligands, provides a biocompatible, substantially non-immunogenic multi-binding compound of this invention. The biological activity of the multi-binding compound is highly sensitive to the valency, geometry, composition, size, flexibility or rigidity, etc. of

the linker as well as the presence or absence of anionic or cationic charge, the relative hydrophobicity/hydrophilicity of the linker, and the like on the linker. In general, the linker may be chosen from any organic molecule construct that orients two or more ligands to the receptors to permit multi-valency. In this regard, the linker can be considered as a "framework" on which the ligands are arranged in order to bring about the desired ligand-orienting result, and thus produce a multi-binding compound.

Ancillary groups which enhance the water solubility/hydrophilicity of the linker and, accordingly, the resulting multi-binding compounds are useful in practicing this invention. Thus, it is within the scope of the present invention to use ancillary groups such as, for example, poly(ethylene glycols), alcohols, polyols, (e.g., glycerin, glycerol propoxylate, saccharides, including mono-, oligo- and polysaccharides, etc.) carboxylates, polycarboxylates, (e.g., polyglutamic acid, polyacrylic acid, etc.), amines, polyamines, (e.g., polylycine, poly(ethyleneimine), and the like) to enhance the water solubility and/or hydrophilicity of the multi-binding compounds of this invention. In preferred embodiments, the ancillary group used to improve water solubility/hydrophilicity will be a polyether. In particularly preferred embodiments, the ancillary group will be a poly(ethylene glycol).

The incorporation of lipophilic ancillary groups within the structure of the linker to enhance the lipophilicity and/or hydrophobicity of the multi-binding compounds described herein is within the scope of this invention. Lipophilic groups useful with the linkers of this invention include, by way of example only, aryl and heteroaryl groups which, as above, may be either unsubstituted or substituted with other groups, but are at least substituted with a group which allows their covalent attachment to the linker. Other lipophilic groups useful with

the linkers of this invention include fatty acid derivatives which do not form bilayers in aqueous medium until higher concentrations are reached.

Also within the scope of this invention is the use of ancillary groups which result in the multi-binding compound being incorporated into a vesicle such as a liposome or a micelle. The term "lipid" refers to any fatty acid derivative that is capable of forming a bilayer such that a hydrophobic portion of the lipid material orients toward the bilayer while a hydrophilic portion orients toward the aqueous phase. Hydrophilic characteristics derive from the presence of phosphato, carboxylic, sulfato, amino, sulfhydryl, nitro and other like groups well known in the art. Hydrophobicity could be conferred by the inclusion of groups that include, but are not limited to, long chain saturated and unsaturated aliphatic hydrocarbon groups of up to 20 carbon atoms and such groups substituted by one or more aryl, heteroaryl, cycloalkyl, and/or heterocyclic group(s). Preferred lipids are phosphoglycerides and sphingolipids, representative examples of which include phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, palmitoyleoyl phosphatidylcholine, lysophosphatidylcholine, lysophosphatidyl-ethanolamine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, distearoyl-phosphatidylcholine or dilinoleoylphosphatidylcholine could be used. Other compounds lacking phosphorus, such as sphingolipid and glycosphingolipid families are also within the group designated as lipid. Additionally, the amphipathic lipids described above may be mixed with other lipids including triglycerides and sterols.

The flexibility of the linker can be manipulated by the inclusion of ancillary groups which are bulky and/or rigid. The presence of bulky or rigid groups can hinder free rotation about bonds in the linker or bonds between the linker and the ancillary group(s) or bonds between the linker and the functional groups. Rigid

groups can include, for example, those groups whose conformational lability is restrained by the presence of rings and/or multiple bonds, for example, aryl, heteroaryl, cycloalkyl and heterocyclic groups. Other groups which can impart rigidity include polypeptide groups such as oligo- or polyproline chains.

Rigidity can also be imparted electrostatically. Thus, if the ancillary groups are either positively or negatively charged, the similarly charged ancillary groups will force the presenter linker into a configuration affording the maximum distance between each of the like charges. The energetic cost of bringing the like-charged groups closer to each other will tend to hold the linker in a configuration that maintains the separation between the like-charged ancillary groups. Further ancillary groups bearing opposite charges will tend to be attracted to their oppositely charged counterparts and potentially may enter into both inter- and intramolecular ionic bonds. This non-covalent mechanism will tend to hold the linker into a conformation which allows bonding between the oppositely charged groups. The addition of ancillary groups which are charged, or alternatively, bear a latent charge when deprotected, following the addition to the linker, include deprotectation of a carboxyl, hydroxyl, thiol or amino protecting group, by a change in pH, oxidation, reduction or other mechanisms known to those skilled in the art, is within the scope of this invention.

Bulky groups can include, for example, large atoms, ions (e.g., iodine, sulfur, metal ions, etc.) or groups containing large atoms, polycyclic groups, including aromatic groups, non-aromatic groups and structures incorporating one or more carbon-carbon multiple bonds (i.e., alkenes and alkynes). Bulky groups can also include oligomers and polymers which are branched- or straight-chain species. Species that are branched are expected to increase the rigidity of the structure more per unit molecular weight gain than are straight-chain species.

In preferred embodiments, rigidity is imparted by the presence of cyclic groups (e.g., aryl, heteroaryl, cycloalkyl, heterocyclic, etc.). In still further preferred embodiments, the ring is an aryl group such as, for example, phenyl or naphthyl. In other preferred embodiments, the linker comprises one or more six-membered rings or crown groups which, while not rigid, retain the conformation of the linker through conformational entropy.

In view of the above, it is apparent that the appropriate selection of a linker group providing suitable orientation, entropy and physico-chemical properties is well within the skill of the art. Eliminating or reducing antigenicity of the multi-binding compounds described herein is also within the scope of this invention.

As explained above, the multi-binding compounds described herein comprise 2-10 ligands for PPARγ and/or RXR, so long as at least one PPARγ ligand is present, attached to a linker that links the ligands in such a manner that they are presented to the PPARγ/RXR receptor complex for multivalent interactions. The linker spatially constrains these interactions to occur within dimensions defined by the linker, thus greatly increasing biological activity of the multi-binding compound as compared to the same number of ligands used in mono-binding form.

The multi-binding compounds of this invention are preferably represented by the empirical formula $(L)_p(X)_q$ where L, X, *p* and *q* are as defined above. This is intended to include the several ways in which the ligands can be linked together in order to achieve the objective of multi-valency, and a more detailed explanation is described below.

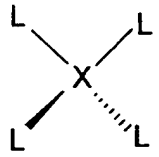
As noted previously, the linker may be considered as a framework to which ligands are attached. Thus, it should be recognized that the ligands can be

attached at any suitable position on this framework, for example, at the termini of a linear chain or at any intermediate position.

The simplest and most preferred multi-binding compound is a bivalent compound which can be represented as L-X-L, where L is a ligand and is the same or different and X is the linker. A trivalent compound could also be represented in a linear fashion, i.e., as a sequence of repeated units L-X-L-X-L, in which L is a ligand and is the same or different at each occurrence, as can X. However, a trimer can also be a multi-binding compound comprising three ligands attached to a central core, and thus represented as $(L)_3X$, where the linker X could include, for example, an aryl or cycloalkyl group. Tetravalent compounds can be represented as, for example, in a linear array:

L-X-L-X-L-X-L

or in a tetrahedral array:

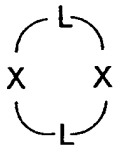


where X and L are as defined herein.

The same considerations apply to higher multibinding compounds of this invention containing 5-10 ligands. However, for multibinding agents attached to a central linker such as aryl or cycloalkyl, there is a self-evident constraint that there must be sufficient attachment sites on the linker to accommodate the number of ligands present; for example, a benzene ring could not directly accommodate more

than 6 ligands, whereas a multi-ring linker (e.g., biphenyl) could accommodate a larger number of ligands.

Certain of the above described compounds may alternatively be represented as cyclic chains of the form:



and variants thereof.

All of the above variations are intended to be within the scope of the invention defined by the formula $(L)_p(X)_q$.

In view of the above description of the linker, it is understood that the term "linker" when used in combination with the term "multibinding compound" includes both a covalently contiguous single linker (e.g., L-X-L) and multiple covalently non-contiguous linkers (L-X-L-X-L) within the multibinding compound.

Preparation of Multibinding Compounds

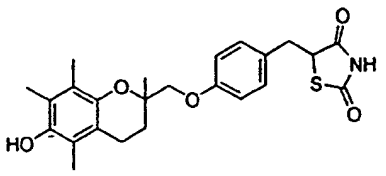
The multibinding compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

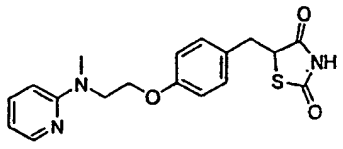
Any compound which acts as a ligand toward PPARγ and/or RXR can be used as a ligand in this invention. As discussed in further detail below, numerous such ligands are known in the art and any of these known compounds or derivatives thereof may be employed as ligands in this invention. Such known ligands are now further described.

Known PPAR ligands include those illustrated below:

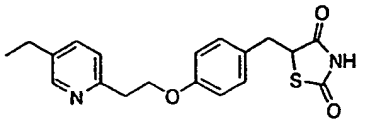
PPAR Ligands



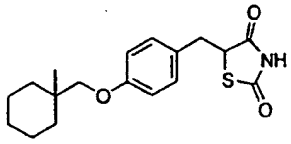
Troglitazone



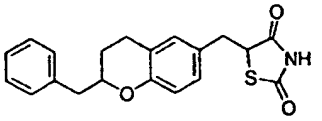
Rosiglitazone



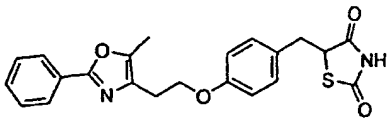
Pioglitazone



Ciglitazone



Englitazone



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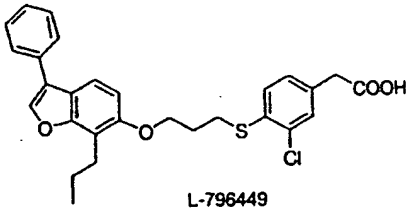
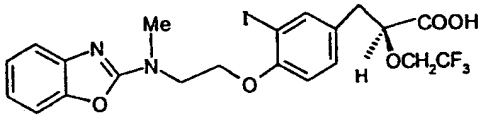
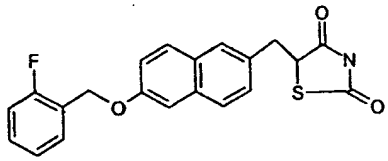


L-796449

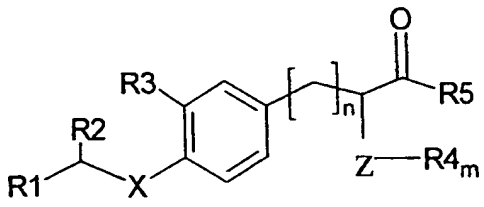


SB219994



MCC-555

The known PPAR ligands suitable for use in the invention generally fall into the following generic formulas A-E:



(A)

wherein

R1 is selected from OH, alkyl, substituted alkyl, alkoxy, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, aryloxy, heteroaryl, and substituted heteroaryl;

R2 is selected from hydrogen or alkyl;

R3 is selected from hydrogen, alkyl, substituted alkyl, I, Br, Cl or F;

R4 is selected from alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

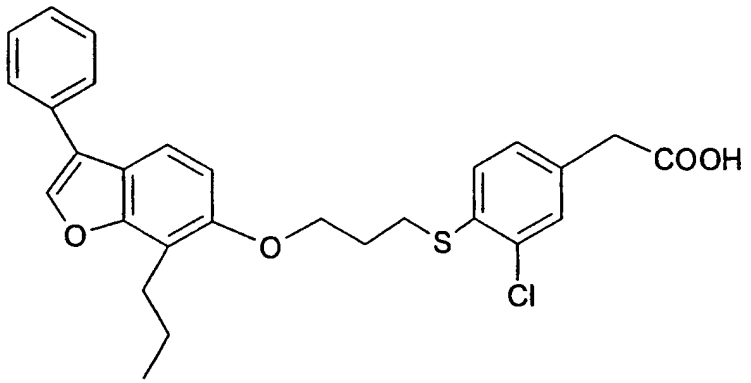
R5 is H, OH, NH_2, or alkoxy, or R4 and R5 together form -C(O)-NH-;

X is -O-, $-CH_2-$, -CH-, -S-, or -NH-; where X is O, R2 and R3 together form $-CH_2-CH_2-$; where X is -CH-, R2 and R3 together form =CH-CH= creating a benzene ring; and

Z is S, NH, H, $-CH_2-$, alkyl, or substituted alkyl; where Z is H, alkyl or substituted alkyl, m=0; else m is 1;

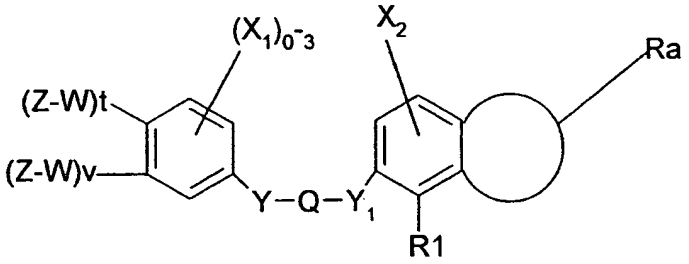
n is 0 or 1;

and derivatives thereof;



(B)

and derivatives thereof;



(C)

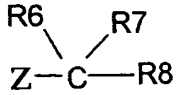
wherein:

R is selected from the group consisting of H, C1-6 alkyl, C5-10 aryl, and C5-10 heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of Ra;

R1 is selected from a group consisting of: H, C1-15 alkyl, C2-15 alkenyl, C2-15 alkynyl and C3-10 cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of Ra;

R3 is selected from a group consisting of: H, NHR1, NHacyl, C1-15 alkyl, C3-10 cycloalkyl, C2-15 alkenyl, C1-15 alkoxy, CO2 alkyl, OH, C2-15 alkynyl, C5-10 aryl, C5-10 heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of Ra;

(Z--W--) is Z--CR6 R7 --, Z--CH=CH--, or



R8 is selected from the group consisting of CR6 R7, O, NR6, and $S(O)_p$;

R6 and R7 are independently selected from the group consisting of H, C1-6 alkyl;

B is selected from the group consisting of:

1) a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 1 heteroatom selected from the group consisting of O, S and N, heteroatom being substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of Ra;

2) a 5 or 6 membered carbocycle containing 0 to 2 double bonds, the carbocycle optionally unsubstituted or substituted with 1 to 3 groups of Ra at any position on the five or six membered carbocycle; and

3) a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 3 heteroatoms selected from the group consisting of O, N, and S, which are substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of Ra;

X1 and X2 are independently selected from a group consisting of: H, OH, C1-15 alkyl, C2-15 alkenyl, C2-15 alkynyl, halo, OR3, $ORCF_3$, C5-10 aryl, C5-10 aralkyl, C5-10 heteroaryl and C1-10 acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of Ra;

Ra represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF3, OCF3, --O--, CN, NO_2, R3, OR3 ; SR3, =N(OR), S(O)R3, SO_2R3, NR3, R3, NR3 COR3, $NR3CO_2R3$, $NR3CON(R3)_2$, $NR3SO_2R3$, COR3, CO_2R3, $CON(R3)_2$, $SO_2N(R3)_2$, $OCON(R3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

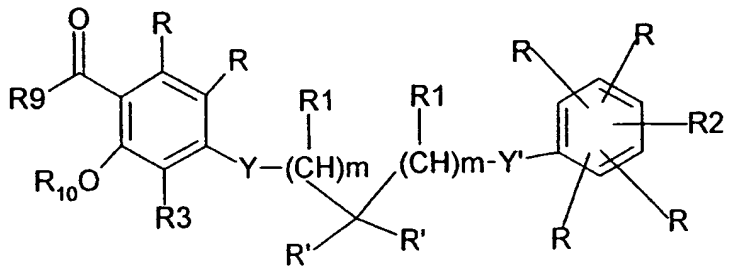
Y is selected from the group consisting of: S(O)p, --CH2 --, --C(O)--, --C(O)NH--, --NR--, --O--, $--SO_2NH$, $--NHSO_2$;

Y1 is selected from the group consisting of: O and C;

Z is selected from the group consisting of: CO_2R3, $R3CO_2R3$, $CONHSO_2Me$, $CONH_2$ and 5-(1H-tetrazole);

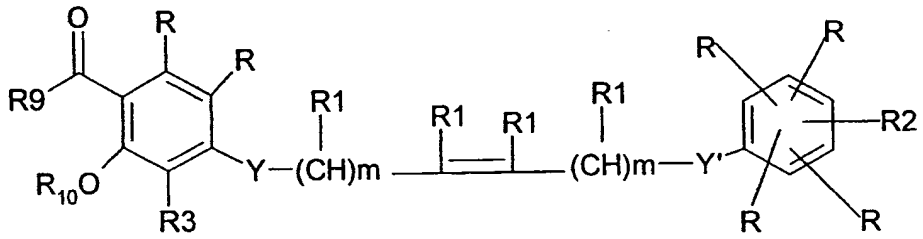
t and v are independently 0 or 1 such that t+v=1;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and p is 0-2 with the proviso when Z is CO_2R3 and B is a 5 membered heterocycle consisting of O, R3 does not represent methyl, as illustrated in US Patent No. 5,869,051, incorporates herein in its entirety by reference, and derivatives thereof; and



(D)

or

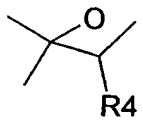


(E)

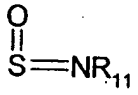
wherein:

each R is independently H, OH, alkyl of 1 to 6 carbon atoms which may be straight chain or branched; alkenyl of 2 to 6 carbon atoms which may be straight chain or branched; trifluoromethyl; alkoxy of 1 to 6 carbon atoms which may be straight chain or branched; SH; thioalkyl of 1 to 6 carbon atoms which may be straight chain or branched; phenyl; phenyl substituted by alkyl of 1 to 3 carbon atoms or by halogen; benzyl; phenethyl; halogen, amino; $N(R4)_2$ wherein R4 is H or alkyl of 1 to 6 carbon atoms which may be straight chain or branched; COOR4; CH_2OR4 ; formyl; CN; trifluoromethylthio; or nitro;

each R' is independently R4 ; OR4 ; COOR4 ; $N(R4)_2$; SR4 ; CH_2OR4; CHO; or together R' and R' are O; CH_2 ; or

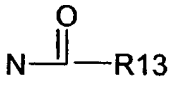


Y' is sulfur, sulfoxide,sulfone;



R11 is H, alkyl of 1-4 carbon atoms which may be straight chain or branched; alkanoyl of 1-4 carbon atoms which may be straight chain or branched; phenylsulfonyl; tosyl; NR12 wherein R12 is H, alkyl of 1-4 carbon atoms which may be straight chain or branched;

or



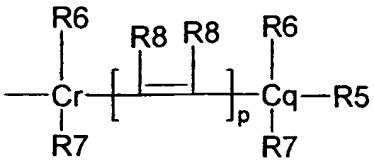
wherein R13 is alkyl of 1-4 carbon atoms which may be straight chain or branched, alkoxy of 1-4 carbon atoms which may be straight chain or branched; N--CN, CH_2, or C=O;

Y is Y' and oxygen;

each R1 is independently hydrogen or alkyl of 1-3 carbon atoms;

each m is independently an integer from 0-6;

R2 is

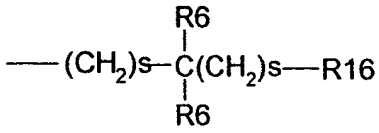


each R6 is independently H or alkyl of 1-4 carbons;

each R7 is independently H, OH, or alkyl of 1-4 carbons;

each R8 is independently H, or alkyl of 1-4 carbons, and is absent when a triple bond is present;

R5 is COOR4 ; CH_2OH; CHO; tetrazole; $NHSO_2R14$; hydroxymethylketone; CN; $CON(R7)_2$; a monocyclic or bicyclic heterocyclic ring containing an acidic hydroxyl group; or COOR15 where R15 is



wherein each s is independently 0-3;

R16 is A) a monocyclic or bicyclic heterocyclic radical containing from 3 to 12 nuclear carbon atoms and 1 or 2 nuclear heteroatoms selected from N and S with at least one being N, and with each ring in the heterocyclic radical being formed of 5 or 6 atoms, or

B) the radical W--R17 wherein W is O, S or NH and R17 contains up to 21 carbon atoms and is (1) a hydrocarbon radical or (2) an acyl radical of an organic acyclic or monocyclic carboxylic acid containing not more than 1 heteroatom in the ring;

R14 is OH, alkyl or alkoxy of 1 to 6 carbon atoms, phenyl or phenyl substituted by alkyl or alkoxy groups of 1 to 3 carbon atoms, halogen, hydroxy, haloalkyl, COOH, CN, formyl, acyl of 1 to 6 carbon atoms or perfluoroalkyl of 1 to 4 carbon atoms;

r and q are each independently 0-20 provided that the total of r and q does not exceed 20;

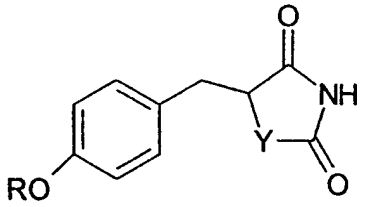
p is 0 or 1;

R9 is alkyl of 1 to 6 carbon atoms which may be straight chain or branched; alkoxy of 1 to 6 carbon atoms which may be straight chain or branched; or $(CH_2)_rR5$; and

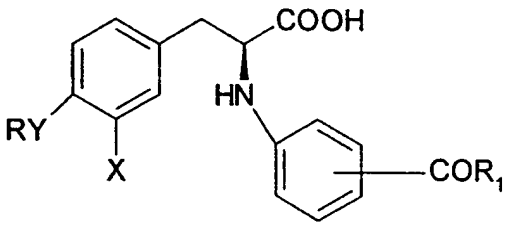
R10 is H; alkyl of 1 to 6 carbon atoms which may be straight chain or branched; $R_4C(O)$ or $R4OCH_2$,

as described in US Patent No. 5,847,008, incorporated herein in its entirety by reference, and derivatives thereof.

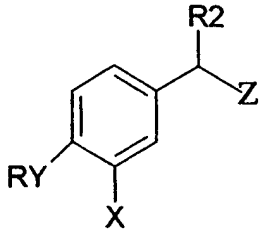
Some derivative structures of the above generic PPAR ligands which may be used in prepartion of the invention are as follows:



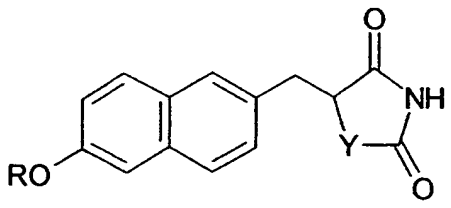
F



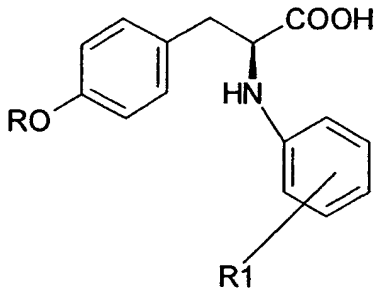
G



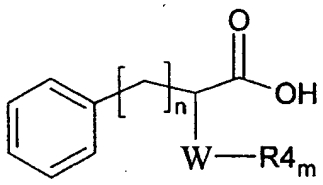
H



I



J



K

wherein

R is selected from alkyl, substituted alkyl, alkaryl, acyl, acylamino, cycloalkyl, heterocyclic, aryl, substituted aryl, and heteroaryl;

R1 is selected from alkyl, substituted alkyl, alkaryl, acyl, acylamino, cycloalkyl, heterocyclic, aryl, substituted aryl, and heteroaryl, and preferably R1 is an the ortho position;

R2 is selected from alkyl, substituted alkyl and hydrogen;

R4 is selected from alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

m is 0 when W is H, alkyl or substituted alkyl; else m is 1.

W is selected from S, NH, H, -CH_2-, alkyl, or substituted alkyl

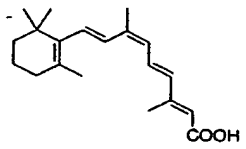
X is selected from I, F, Cl, Br, H, alkyl, and substituted alkyl;

Y is selected from S, O and N;

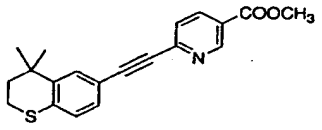
Z is selected from the group consisting of: C(O)H, CO_2R3, $R3CO_2R3$, $CONHSO_2Me$, $CONH_2$ and 5-(1H-tetrazole); wherein R3 is selected from a group consisting of: H, NHR1, NHacyl, C1-15 alkyl, C3-10 cycloalkyl, C2-15 alkenyl, C1-15 alkoxy, CO_2 alkyl, OH, C2-15 alkynyl, C5-10 aryl, C5-10 heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of Ra; and wherein Ra represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, --O--, CN, NO_2, R3, OR3; SR3, =N(OR), S(O)R3, SO_2R3, NR3, R3, NR3 COR3, $NR3CO_2R3$, $NR3CON(R3)_2$, $NR3SO_2R3$, COR3, CO_2R3, $CON(R3)_2$, $SO_2N(R3)_2$, $OCON(R3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl.

Suitable RXR ligands for use in the invention may include known RXR ligands such as the following:

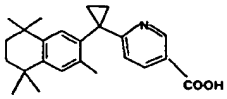
RXR Ligands



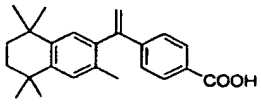
Panretin



Tazoretene

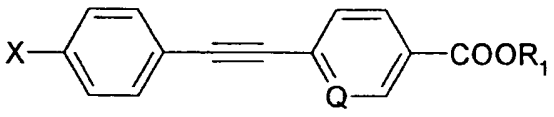


LG100268

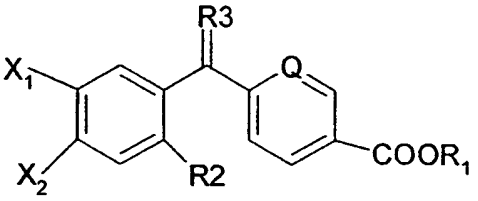


Tagretin

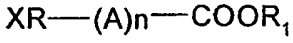
Derivatives of RXR ligands may also be used in preparation of the invention. Such derivatives may be selected from one or more of the following formulas II-IV:



(II)



(III)



(IV)

wherein

X, X1 and X2 are independently selected from the group consisting of H, OH, I, Br, Cl, F, Na, SH, O, NH, carbonyl, amide, alkyl, alkoxy, aryl, aryloxy, and alkaryl;

R is aryl, substituted aryl, alkyl, substituted alkyl, heteroaryl, or substituted heteroaryl;

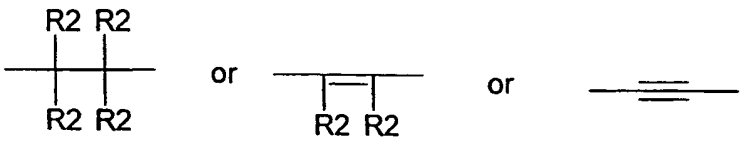
R1 is H or alkyl;

R2 is H or alkyl;

R3 is CH_2, O, or NOR4 wherein R4 is alkyl or substituted alkyl;

Q is CH or N,

A is



and n is 1-10.

Other RXR and PPARγ ligands and derivatives may be known to those in the art. Preferentially, RXR and PPARγ ligands or derivatives thereof used in the invention are preferentially bound to only the RXR or PPARγ receptor, respectively. In particular, it is preferred that the PPAR ligand or derivative thereof preferentially bind only to the PPARγ receptor.

Activation of the RXR receptor with known RXR ligands can lead to modulation of the transcriptional activity of a wide variety of RXR/nuclear receptor complexes. Thus, the activation of the RXR receptor by the use of RXR ligands may potentiate many other effects within the body. Because of this lack of functional specificity, use of a modified RXR ligand as set forth above to control transcription exclusivity by the PPARγ/RXR heterodimer is preferred. Preferentially, the RXR ligands used in the invention are a derivative of known RXR ligands exhibiting more limited functionality and less independent activation of, or lower binding affinity for, other RXR/nuclear receptor complexes which are not of interest.

In contrast, many known PPARγ ligands are very specific in that they bind preferentially to only the PPARγ receptor. These ligands, some of which are exemplified herein, and derivatives of other known PPAR agonists selected for preferential binding to the PPARγ receptor, may be used herein.

It is known that fatty acids, eicosanoids, prostaglandins and metabolites thereof activate PPARγ, as do non-steroidal anti-inflammatory drugs (NSAIDS). Although fatty acids such as 15 deoxy $D^{12,14}$ PGJ_2, linoleic acid, γ-linolenic acid, oleic acid, stearic acid, cis-pariniaric acid, eicosopentonoic acid ad decosahexanoic acid bind well to the PPARγ receptor, they are not specific to the PPARγ

receptor. The NSAIDS are not specific and also may have a low affinity for the PPARγ receptor. Therefore, because these compounds activate one or more of the PPAR receptors, including both PPARγ and PPARα, as well as potentially other receptors, they prompt too broad a response causing potentially undesirable reactions and side effects. Therefore, these would not form acceptable ligands for the invention described herein, although derivatives thereof may be identified which would preferentially bind to the PPARγ receptor and therefore could be used in the invention described herein.

In contrast, the class of drugs known as thiazolidinediones (TZDs) are highly selective for PPARγ. TZDs or "glitazones" are high-affinity agonists of PPARγ. The glitazones enhance the sensitivity of target tissues to insulin while reducing serum insulin and lipid levels, as well as reducing plasma levels of free fatty acids, triglycerides and total cholesterol in mammals having Type 2 diabetes, which affects the proper storage and utilization of energy in the body in the form of glucose. NIDDM is characterized by high plasma glucose levels, insulin resistance, and insufficient insulin secretion by the β-cells of the pancreas. Drug treatment of NIDDM classically focuses on increasing insulin secretion, creating a condition of hyperinsulemia which creates a risk of heart disease. Some TZDs cause increases in plasma volume, increased adipose cell formation in bone marrow at high doses, and are known to have a hepatatoxic effect. Further some TZDs lack potency for the PPARγ receptor, therefore requiring high patient doses or frequent patient dosing, and potentially leading to non-mechanism (i.e., non-PPARγ binding) related side effects or toxicities. **Diabetes** Vol. 47, (1998) 507-514. Therefore, although TZDs may be used as ligands for the invention described herein, derivatives thereof may be desired.

Further herein, the PPARγ ligand or ligand derivatives suitable for use in the invention A-K are referred to as L1-L11, and the RXR ligands or derivatives thereof II-IV are referred to as L12-14.

Combinatorial Libraries

Combinatorial approaches for identifying multimeric compounds which possess multibinding properties will now be discussed.

Specifically, factors such as the proper juxtaposition of the individual ligands of a multibinding compound with respect to the relevant array of binding sites on a target or targets is important in optimizing the interaction of the multibinding compound with its target(s) and to maximize the biological advantage through multivalency. One approach is to identify a library of candidate multibinding compounds with properties spanning the multibinding parameters that are relevant for a particular target. These parameters include: (1) the identity of ligand(s), (2) the orientation of ligands, (3) the valency of the construct, (4) linker length, (5) linker geometry, (6) linker physical properties, and (7) linker chemical functional groups.

Libraries of multimeric compounds potentially possessing multibinding properties (i.e., candidate multibinding compounds) and comprising a multiplicity of such variables are prepared and these libraries are then evaluated via conventional assays corresponding to the ligand selected and the multibinding parameters desired. Considerations relevant to each of these variables are set forth below.

Selection of ligand(s)

A single ligand or set of ligands is (are) selected for incorporation into the libraries of candidate multibinding compounds which library is directed against a

particular biological target or targets. The only requirement for the ligands chosen is that they are capable of interacting with the selected target(s). Thus, ligands may be known drugs, modified forms of known drugs, substructures of known drugs or substrates of modified forms of known drugs (which are competent to interact with the target), or other compounds. Ligands are preferably chosen based on known favorable properties that may be projected to be carried over to or amplified in multibinding forms. Favorable properties include demonstrated safety and efficacy in human patients, ability to increase insulin sensitivity, ability to lower serum triglyceride, cholesterol and/or fatty acid levels, etc. However, it is crucial to note that ligands which display an unfavorable property from among the previous list may obtain a more favorable property through the process of multibinding compound formation; i.e., ligands should not necessarily be excluded on such a basis. For example, a ligand that is not sufficiently potent at a particular target so as to be efficacious in a human patient may become highly potent and efficacious when presented in multibinding form. A ligand that is potent and efficacious but not of utility because of a non-mechanism-related toxic side effect may have increased therapeutic index (increased potency relative to toxicity) as a multibinding compound. Compounds that exhibit short *in vivo* half-lives may have extended half-lives as multibinding compounds. Physical properties of ligands that limit their usefulness (e.g. poor bioavailability due to low solubility, hydrophobicity, hydrophilicity) may be rationally modulated in multibinding forms, providing compounds with physical properties consistent with the desired utility.

Orientation: selection of ligand attachment points and linking chemistry

Several points are chosen on each ligand at which to attach the ligand to the linker. The selected points on the ligand/linker for attachment are functionalized to contain complementary reactive functional groups. This permits probing the effects of presenting the ligands to their receptor(s) in multiple relative

orientations, an important multibinding design parameter. The only requirement for choosing attachment points is that attaching to at least one of these points does not abrogate activity of the ligand. Such points for attachment can be identified by structural information when available. Alternatively, evaluation of ligand/target binding by nuclear magnetic resonance will permit the identification of sites non-essential for ligand/target binding. See, for example, Fesik, et al., U.S. Patent No. 5,891,643. When such structural information is not available, utilization of structure-activity relationships (SAR) for ligands will suggest positions where substantial structural variations are and are not allowed. In the absence of both structural and SAR information, a library is merely selected with multiple points of attachment to allow presentation of the ligand in multiple distinct orientations. Subsequent evaluation of this library will indicate what positions are suitable for attachment.

It is important to emphasize that positions of attachment that do abrogate the activity of the monomeric ligand may also be advantageously included in candidate multibinding compounds in the library provided that such compounds bear at least one ligand attached in a manner which does not abrogate intrinsic activity. This selection derives from, for example, heterobivalent interactions within the context of a single target molecule. For example, consider a receptor antagonist ligand bound to its target receptor, and then consider modifying this ligand by attaching to it a second copy of the same ligand with a linker which allows the second ligand to interact with the same receptor molecule at sites proximal to the antagonist binding site, which include elements of the receptor that are not part of the formal antagonist binding site and/or elements of the matrix surrounding the receptor such as the membrane. Here, the most favorable orientation for interaction of the second ligand molecule with the receptor/matrix may be achieved by attaching it to the linker at a position which abrogates activity of the ligand at the formal antagonist binding site. Another way to consider this is

that the SAR of individual ligands within the context of a multibinding structure is often different from the SAR of those same ligands in momomeric form.

The foregoing discussion focused on bivalent interactions of dimeric compounds bearing two copies of the same ligand joined to a single linker through different attachment points, one of which may abrogate the binding/activity of the monomeric ligand. It should also be understood that bivalent advantage may also be attained with heterodimeric constructs bearing two different ligands that bind to common or different targets. For example, a PPARγ receptor agonist and an RXR receptor agonist may be joined to a linker through attachment points which do not abrogate the binding affinity of the monomeric ligands for their respective receptor sites. The dimeric compound may achieve enhanced affinity for both receptors due to favorable interactions between the PPARγ ligand and elements of the RXR receptor proximal to the formal RXR agonist binding site and between the RXR ligand and elements of the PPARγ receptor proximal to the formal PPARγ agonist binding site. Thus, the dimeric compound may be a more potent and selective agonist of insulin sensitivity and a superior therapy for NIDDM, cancer including colon carcinomas and lipocarcinomas, hyperlipedemia, arteriosclerosis and inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.

Once the ligand attachment points have been chosen, one identifies the types of chemical linkages that are possible at those points. The most preferred types of chemical linkages are those that are compatible with the overall structure of the ligand (or protected forms of the ligand), readily and generally formed, stable and intrinsically innocuous under typical chemical and physiological conditions, and compatible with a large number of available linkers. Amide bonds, ethers, amines, carbamates, ureas, and sulfonamides are but a few examples of preferred linkages.

Linkers: spanning relevant multibinding parameters through selection of valency, linker length, linker geometry, rigidity, physical properties, and chemical functional groups

In the library of linkers employed to generate the library of candidate multibinding compounds, the selection of linkers employed in this library of linkers takes into consideration the following factors.

Valency. In most instances the library of linkers is initiated with divalent linkers. The choice of ligands and proper juxtaposition of two ligands relative to their binding sites permits such molecules to exhibit target binding affinities and specificities more than sufficient to confer biological advantage. Furthermore, divalent linkers or constructs are also typically of modest size such that they retain the desirable biodistribution properties of small molecules.

Linker length. Linkers are chosen in a range of lengths to allow the spanning of a range of inter-ligand distances that encompass the distance preferable for a given divalent interaction. In some instances the preferred distance can be estimated rather precisely from high-resolution structural information of targets, typically enzymes and soluble receptor targets. In other instances where high-resolution structural information is not available, one can make use of simple models to estimate the maximum distance between binding sites either on adjacent receptors or at different locations on the same receptor. In situations where two binding sites are present on the same target (or target subunit for multisubunit targets), preferred linker distances are 2-20 Å, with more preferred linker distances of 3-12 Å. In situations where two binding sites reside on separate (e.g., protein) target sites, preferred linker distances are 20-100 Å, with more preferred distances of 30-70 Å.

Linker geometry and rigidity. The combination of ligand attachment site, linker length, linker geometry, and linker rigidity determine the possible ways in which the ligands of candidate multibinding compounds may be displayed in three dimensions and thereby presented to their binding sites. Linker geometry and rigidity are nominally determined by chemical composition and bonding pattern, which may be controlled and are systematically varied as another spanning function in a multibinding array. For example, linker geometry is varied by attaching two ligands to the ortho, meta, and para positions of a benzene ring, or in *cis*- or *trans*-arrangements at the 1,1- vs. 1,2- vs. 1,3- vs. 1,4- positions around a cyclohexane core or in *cis*- or *trans*-arrangements at a point of ethylene unsaturation. Linker rigidity is varied by controlling the number and relative energies of different conformational states possible for the linker. For example, a divalent compound bearing two ligands joined by 1,8-octyl linker has many more degrees of freedom, and is therefore less rigid than a compound in which the two ligands are attached to the 4,4' positions of a biphenyl linker.

Linker physical properties. The physical properties of linkers are nominally determined by the chemical constitution and bonding patterns of the linker, and linker physical properties impact the overall physical properties of the candidate multibinding compounds in which they are included. A range of linker compositions is typically selected to provide a range of physical properties (hydrophobicity, hydrophilicity, amphiphilicity, polarization, acidity, and basicity) in the candidate multibinding compounds. The particular choice of linker physical properties is made within the context of the physical properties of the ligands they join and, preferably, the goal is to generate molecules with favorable properties. For example, linkers can be selected to avoid those that are too hydrophilic or too hydrophobic to be readily absorbed and/or distributed *in vivo*.

Linker chemical functional groups. Linker chemical functional groups are selected to be compatible with the chemistry chosen to connect linkers to the ligands and to impart the range of physical properties sufficient to span initial examination of this parameter.

Combinatorial synthesis

Having chosen a set of *n* ligands (*n* being determined by the sum of the number of different attachment points for each ligand chosen) and *m* linkers by the process outlined above, a library of (*n*!)*m* candidate divalent multibinding compounds is prepared which spans the relevant multibinding design parameters for a particular target. For example, an array generated from two ligands, one which has two attachment points (A1, A2) and one which has three attachment points (B1, B2, B3) joined in all possible combinations provide for at least 15 possible combinations of multibinding compounds:

A1-A1	A1-A2	A1-B1	A1-B2	A1-B3	A2-A2	A2-B1	A2-B2
A2-B3	B1-B1	B1-B2	B1-B3	B2-B2	B2-B3	B3-B3	

When each of these combinations is joined by 10 different linkers, a library of 150 candidate multibinding compounds results.

Given the combinatorial nature of the library, common chemistries are preferably used to join the reactive functionalities on the ligands with complementary reactive functionalities on the linkers. The library therefore lends itself to efficient parallel synthetic methods. The combinatorial library can employ solid phase chemistries well known in the art wherein the ligand and/or linker is attached to a solid support. Alternatively and preferably, the combinatorial library is prepared in the solution phase. After synthesis, candidate multibinding

compounds are optionally purified before assaying for activity by, for example, chromatographic methods (e.g., HPLC).

Analysis of array by biochemical, analytical, pharmacological, and computational methods

Various methods are used to characterize the properties and activities of the candidate multibinding compounds in the library to determine which compounds possess multibinding properties. Physical constants such as solubility under various solvent conditions and logD/clogD values are determined. A combination of NMR spectroscopy and computational methods is used to determine low-energy conformations of the candidate multibinding compounds in fluid media. The ability of the members of the library to bind to the desired target and other targets is determined by various standard methods, which include radioligand displacement assays for receptor and ion channel targets, and kinetic inhibition analysis for many enzyme targets. *In vitro* efficacy, such as for receptor agonists and antagonists, ion channel blockers, and antimicrobial activity are also determined. Pharmacological data, including oral absorption, everted gut penetration, other pharmacokinetic parameters and efficacy data are determined in appropriate models. In this way, key structure-activity relationships are obtained for multibinding design parameters which are then used to direct future work.

The members of the library which exhibit multibinding properties, as defined herein, can be readily determined by conventional methods. First, those members which exhibit multibinding properties are identified by conventional methods as described above, including conventional assays (both *in vitro* and *in vivo*).

Second, ascertaining the structure of those compounds which exhibit multibinding properties can be accomplished via art recognized procedures. For

example, each member of the library can be encrypted or tagged with appropriate information allowing determination of the structure of relevant members at a later time. See, for example, Dower, et al., International Patent Application Publication No. WO 93/06121; Brenner, et al., Proc. Natl. Acad. Sci., USA, 89:5181 (1992); Gallop, et al., U.S. Patent No. 5,846,839; each of which is incorporated herein by reference in its entirety. Alternatively, the structure of relevant multivalent compounds can also be determined from soluble and untagged libraries of candidate multivalent compounds by methods known in the art, such as those described by Hindsgaul, et al., Canadian Patent Application No. 2,240,325 which was published on July 11, 1998. Such methods couple frontal affinity chromatography with mass spectroscopy to determine both the structure and relative binding affinities of candidate multibinding compounds to receptors.

The process set forth above for dimeric candidate multibinding compounds can, of course, be extended to trimeric candidate compounds and higher analogs thereof.

Follow-up synthesis and analysis of additional array(s)

Based on the information obtained through analysis of the initial library, an optional component of the process is to ascertain one or more promising multibinding "lead" compounds as defined by particular relative ligand orientations, linker lengths, linker geometries, etc. Additional libraries can then be generated around these leads to provide for further information regarding structure to activity relationships. These arrays typically bear more focused variations in linker structure to further optimize target affinity and/or activity at the target (antagonism, partial agonism, etc.), and/or alter physical properties. By iterative redesign/analysis using the novel principles of multibinding design along with classical medicinal chemistry, biochemistry, and pharmacology approaches,

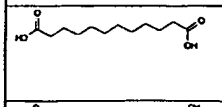
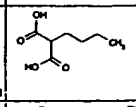
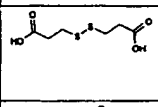
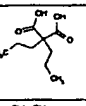
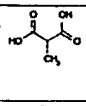
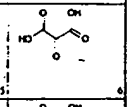
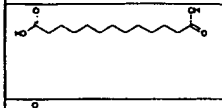
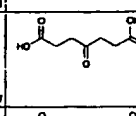
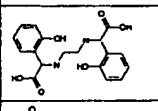
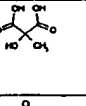
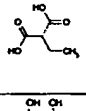
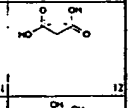
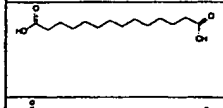
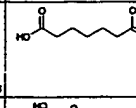
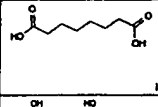
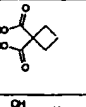
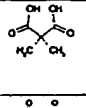
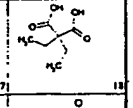
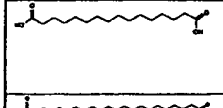
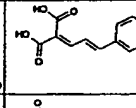
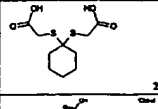
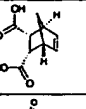
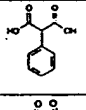
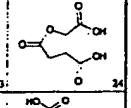
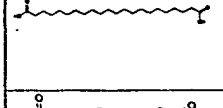
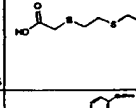
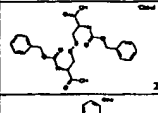
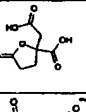
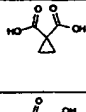
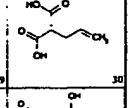
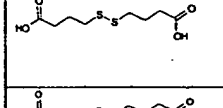
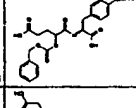
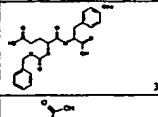
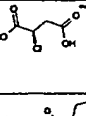
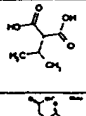
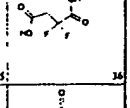
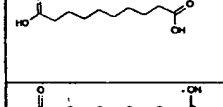
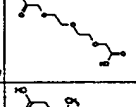
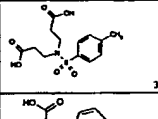
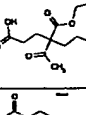
one is able to prepare and identify optimal multibinding compounds that exhibit biological advantage towards their targets and as therapeutic agents.

To further elaborate upon this procedure, suitable divalent linkers include, by way of example only, those derived from dicarboxylic acids, disulfonylhalides, dialdehydes, dipseudohalides, diketones, dihalides, diisocyanates, diamines, diols, diboronates, mixtures of carboxylic acids, sulfonylhalides, aldehydes, ketones, halides, isocyanates, amines and diols. In each case, the carboxylic acid, sulfonylhalide, aldehyde, ketone, halide, isocyanate, amine and diol functional group is reacted with a complementary functionality on the ligand to form a covalent linkage. Such complementary functionality is well known in the art as illustrated in the following table, which is exemplary only:

COMPLEMENTARY BINDING CHEMISTRIES

First Reactive Group	Second Reactive Group	Linkage
hydroxyl	isocyanate	urethane
amine	epoxide	β-hydroxyamine
sulfonyl halide	amine	sulfonamide
carboxyl acid	amine	amide
hydroxyl	alkyl/aryl halide	ether
aldehyde	amine/$NaCNBH_4$	amine
ketone	amine/$NaCNBH_4$	amine
amine	isocyanate	carbamate

Exemplary linkers include the following linkers identified as X-1 through X-418 as set forth below in Table 1:

Diacids					
 1	 2	 3	 4	 5	 6
 7	 8	 9	 10	 11	 12
 13	 14	 15	 16	 17	 18
 19	 20	 21	 22	 23	 24
 25	 26	 27	 28	 29	 30
 31	 32	 33	 34	 35	 36
 37	 38	 39	 40	41	42
43	44	45	46	47	48
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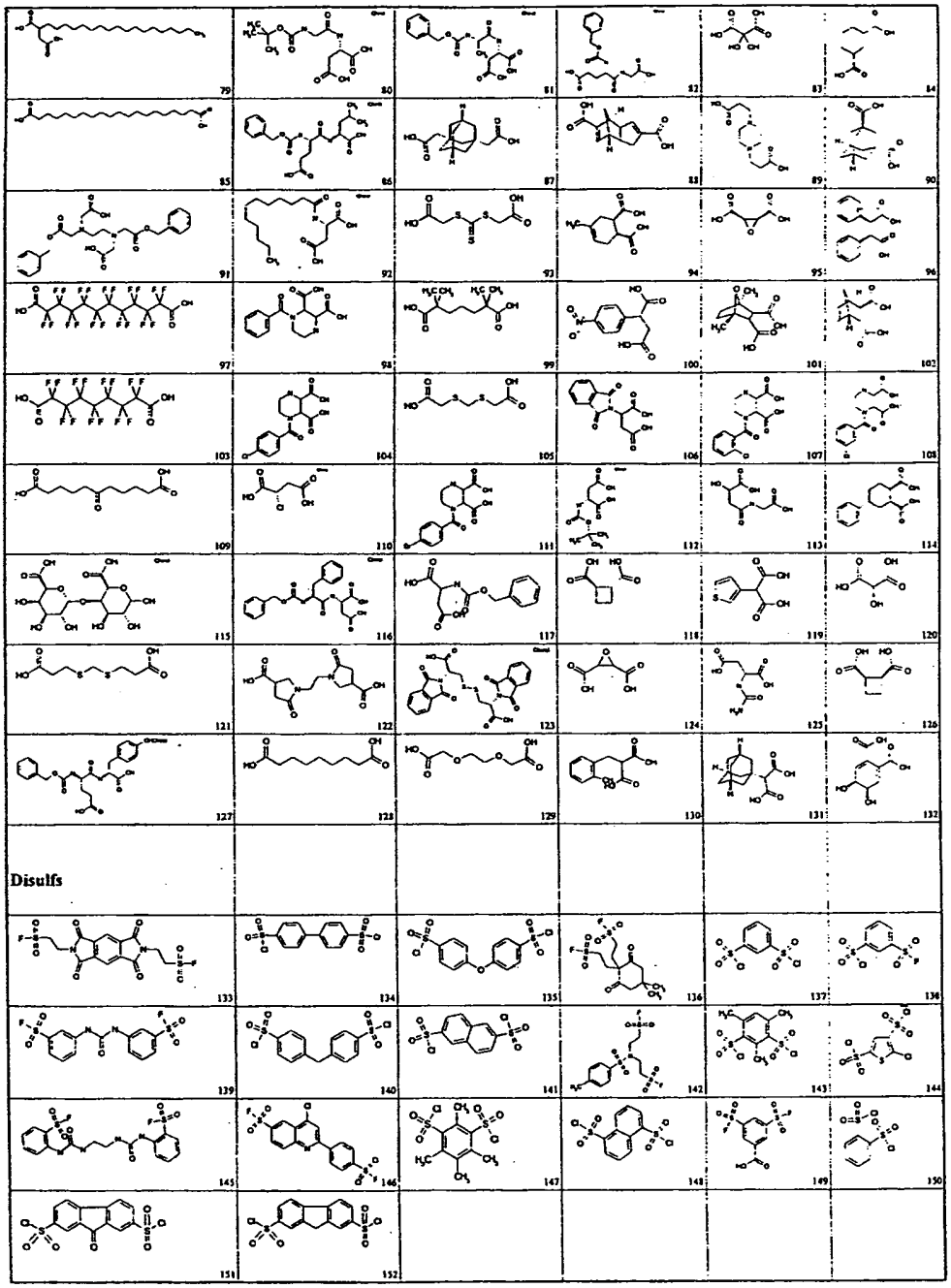
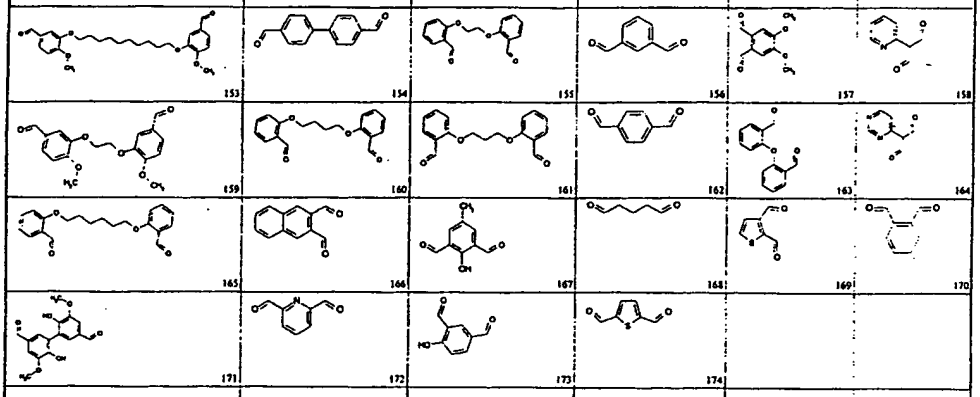
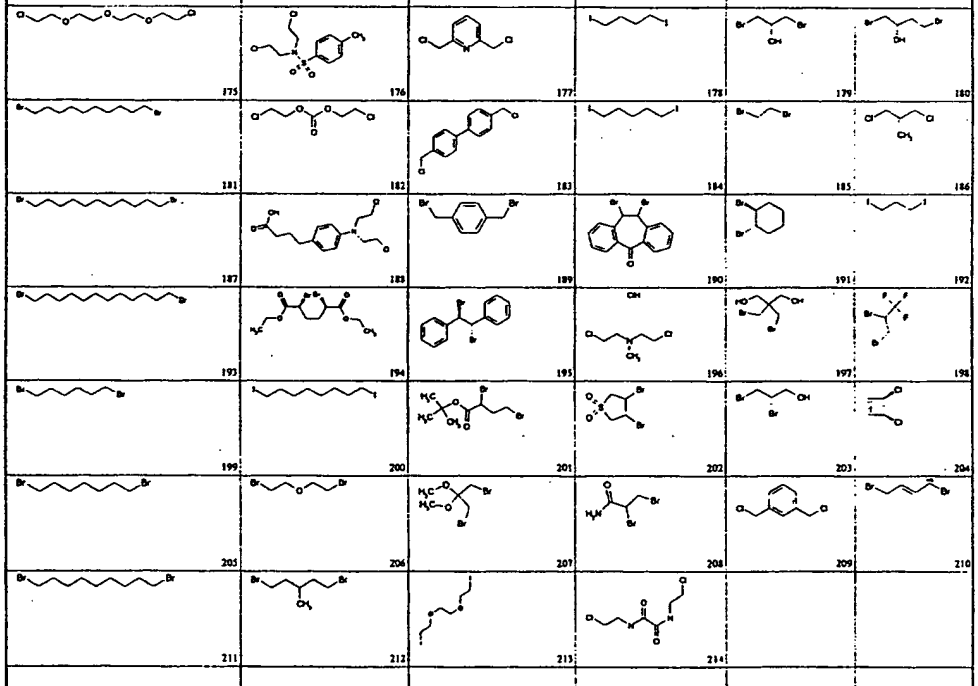
67	68	69	70	71	72
73	74	75	76	77	78


Disulfs

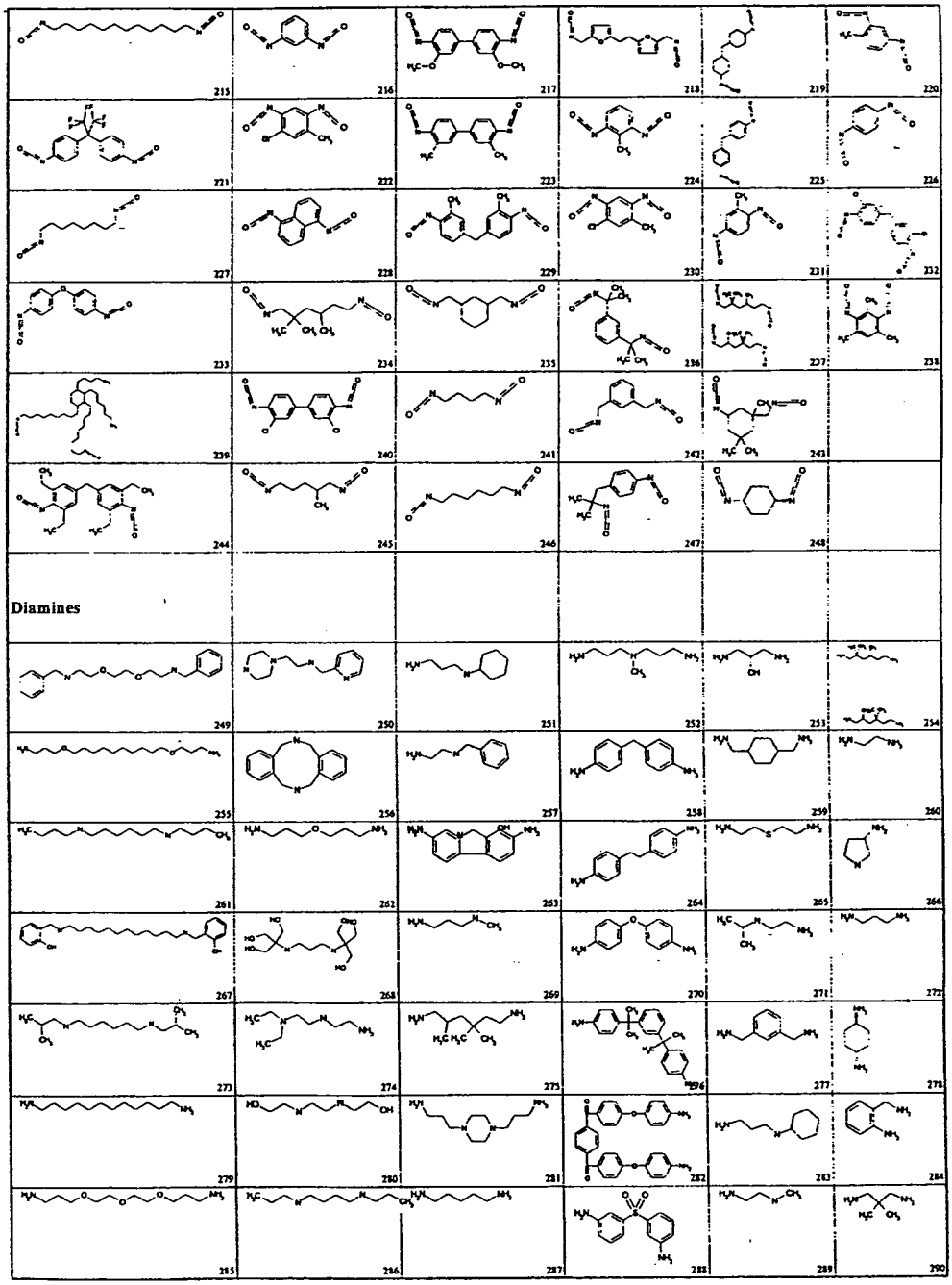
Dialdehydes



Dihalides



Diisocyanates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Diamines
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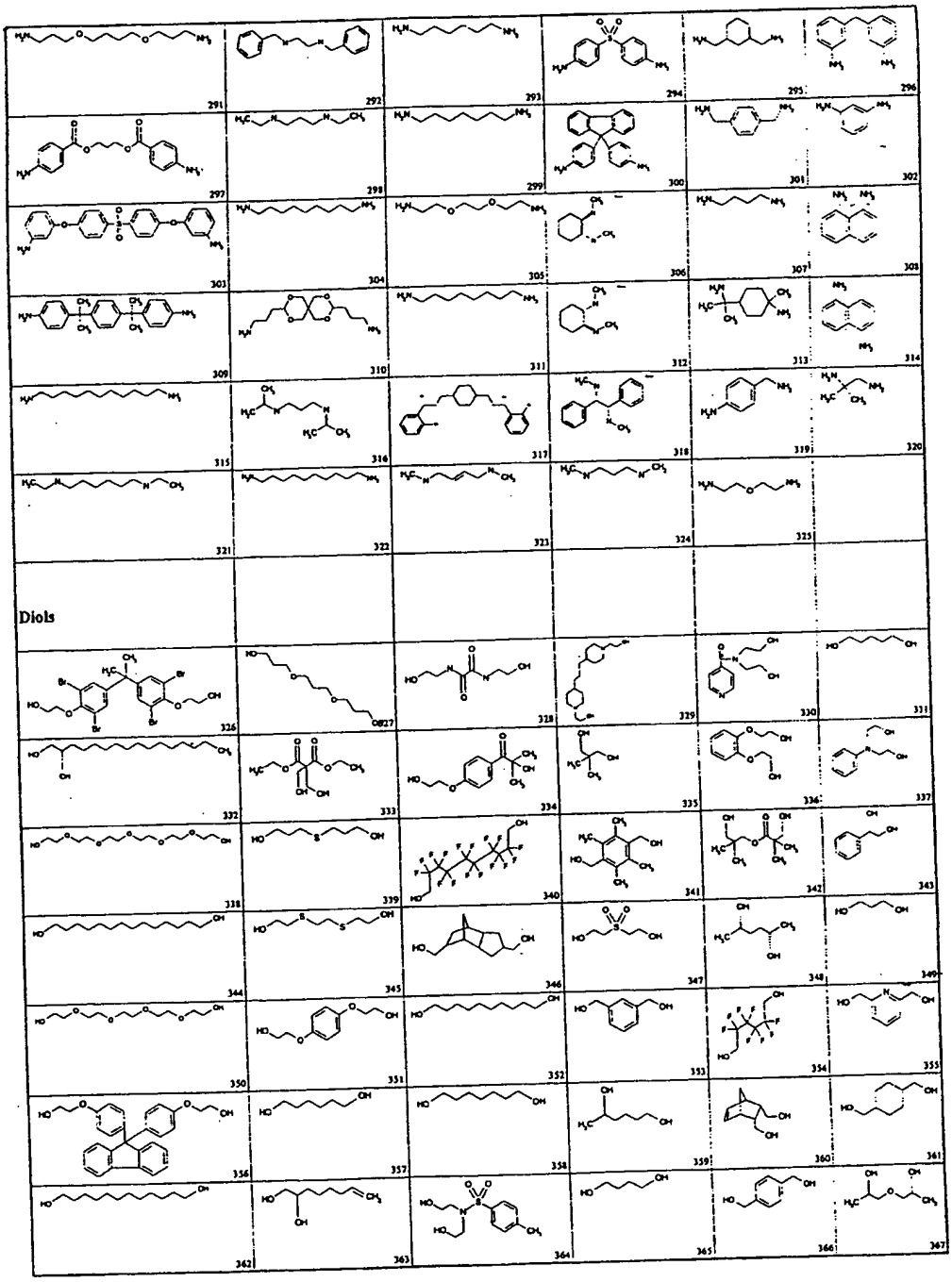
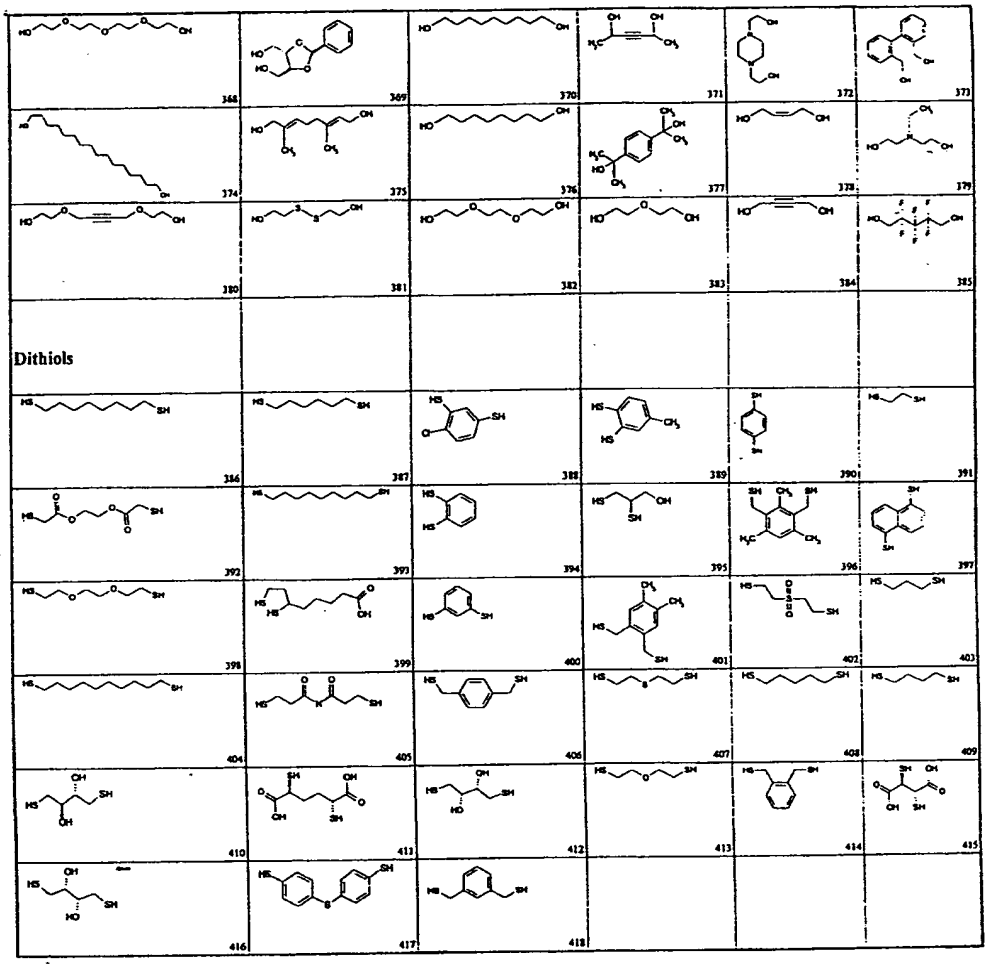

Diols


Dithiols

Representative ligands for use in this invention include, by way of example, L-1 through L-14 as identified above.

Combinations of ligands (L) and linkers (X) per this invention include, by way example only, homo- and hetero-dimers wherein a first ligand is selected from L-1 through L-14 above and the second ligand and linker is selected from the following:

L-1/X-1-	L-1/X-2-	L-1/X-3-	L-1/X-4-	L-1/X-5-	L-1/X-6-
L-1/X-7-	L-1/X-8-	L-1/X-9-	L-1/X-10-	L-1/X-11-	L-1/X-12-
L-1/X-13-	L-1/X-14-	L-1/X-15-	L-1/X-16-	L-1/X-17-	L-1/X-18-
L-1/X-19-	L-1/X-20-	L-1/X-21-	L-1/X-22-	L-1/X-23-	L-1/X-24-
L-1/X-25-	L-1/X-26-	L-1/X-27-	L-1/X-28-	L-1/X-29-	L-1/X-30-
L-1/X-31-	L-1/X-32-	L-1/X-33-	L-1/X-34-	L-1/X-35-	L-1/X-36-
L-1/X-37-	L-1/X-38-	L-1/X-39-	L-1/X-40-	L-1/X-41-	L-1/X-42-
L-1/X-43-	L-1/X-44-	L-1/X-45-	L-1/X-46-	L-1/X-47-	L-1/X-48-
L-1/X-49-	L-1/X-50-	L-1/X-51-	L-1/X-52-	L-1/X-53-	L-1/X-54-
L-1/X-55-	L-1/X-56-	L-1/X-57-	L-1/X-58-	L-1/X-59-	L-1/X-60-
L-1/X-61-	L-1/X-62-	L-1/X-63-	L-1/X-64-	L-1/X-65-	L-1/X-66-
L-1/X-67-	L-1/X-68-	L-1/X-69-	L-1/X-70-	L-1/X-71-	L-1/X-72-
L-1/X-73-	L-1/X-74-	L-1/X-75-	L-1/X-76-	L-1/X-77-	L-1/X-78-
L-1/X-79-	L-1/X-80-	L-1/X-81-	L-1/X-82-	L-1/X-83-	L-1/X-84-
L-1/X-85-	L-1/X-86-	L-1/X-87-	L-1/X-88-	L-1/X-89-	L-1/X-90-
L-1/X-91-	L-1/X-92-	L-1/X-93-	L-1/X-94-	L-1/X-95-	L-1/X-96-
L-1/X-97-	L-1/X-98-	L-1/X-99-	L-1/X-100-	L-1/X-101-	L-1/X-102-
L-1/X-103-	L-1/X-104-	L-1/X-105-	L-1/X-106-	L-1/X-107-	L-1/X-108-
L-1/X-109-	L-1/X-110-	L-1/X-111-	L-1/X-112-	L-1/X-113-	L-1/X-114-
L-1/X-115-	L-1/X-116-	L-1/X-117-	L-1/X-118-	L-1/X-119-	L-1/X-120-
L-1/X-121-	L-1/X-122-	L-1/X-123-	L-1/X-124-	L-1/X-125-	L-1/X-126-
L-1/X-127-	L-1/X-128-	L-1/X-129-	L-1/X-130-	L-1/X-131-	L-1/X-132-
L-1/X-133-	L-1/X-134-	L-1/X-135-	L-1/X-136-	L-1/X-137-	L-1/X-138-
L-1/X-139-	L-1/X-140-	L-1/X-141-	L-1/X-142-	L-1/X-143-	L-1/X-144-
L-1/X-145-	L-1/X-146-	L-1/X-147-	L-1/X-148-	L-1/X-149-	L-1/X-150-
L-1/X-151-	L-1/X-152-	L-1/X-153-	L-1/X-154-	L-1/X-155-	L-1/X-156-
L-1/X-157-	L-1/X-158-	L-1/X-159-	L-1/X-160-	L-1/X-161-	L-1/X-162-
L-1/X-163-	L-1/X-164-	L-1/X-165-	L-1/X-166-	L-1/X-167-	L-1/X-168-
L-1/X-169-	L-1/X-170-	L-1/X-171-	L-1/X-172-		
L-1/X-173-	L-1/X-174-	L-1/X-175-	L-1/X-176-	L-1/X-177-	L-1/X-178-
L-1/X-179-	L-1/X-180-	L-1/X-181-	L-1/X-182-	L-1/X-183-	L-1/X-184-
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	L-1/X-221-	L-1/X-222-	L-1/X-223-	L-1/X-224-	L-1/X-225-	L-1/X-226-
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	L-2/X-13-	L-2/X-14-	L-2/X-15-	L-2/X-16-	L-2/X-17-	L-2/X-18-
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	L-8/X-97-	L-8/X-98-	L-8/X-99-	L-8/X-100-	L-8/X-101-	L-8/X-102-
	L-8/X-103-	L-8/X-104-	L-8/X-105-	L-8/X-106-	L-8/X-107-	L-8/X-108-
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	L-8/X-227-	L-8/X-228-	L-8/X-229-	L-8/X-230-	L-8/X-231-	L-8/X-232-
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	L-9/X-1-	L-9/X-2-	L-9/X-3-	L-9/X-4-	L-9/X-5-	L-9/X-6-
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L-14/X-413- L-14/X-414- L-14/X-415- L-14/X-416- L-14/X-417- L-14/X-418-

Pharmaceutical Formulations

When employed as pharmaceuticals, the compounds of the invention are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of the invention associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to

provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Preferably, the compound of the invention is employed at no more than about 20 weight percent of the pharmaceutical composition, more preferably no more than about 15 weight percent, with the balance being pharmaceutically inert carrier(s).

The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician or veterinarian, in the light of the relevant

circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous

solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as corn oil, cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The following formulation examples illustrate representative pharmaceutical compositions of the present invention.

Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

Ingredient	Quantity (mg/capsule)
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Formulation Example 2

A tablet formula is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
Active Ingredient	25.0
Cellulose, microcrystalline	200.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Example 3

A dry powder inhaler formulation is prepared containing the following components:

Ingredient	Weight %
Active Ingredient	5
Lactose	95

The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

Ingredient	Quantity (mg/tablet)
Active Ingredient	30.0 mg
Starch	45.0 mg
Microcrystalline cellulose	35.0 mg
Polyvinylpyrrolidone (as 10% solution in sterile water)	4.0 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1.0 mg
Total	120 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

Formulation Example 5

Capsules, each containing 40 mg of medicament are made as follows:

Ingredient	Quantity (mg/capsule)
Active Ingredient	40.0 mg
Starch	109.0 mg
Magnesium stearate	1.0 mg
Total	150.0 mg

The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

Ingredient	Amount
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the

minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 mL dose are made as follows:

Ingredient	Amount
Active Ingredient	50.0 mg
Xanthan gum	4.0 mg
Sodium carboxymethyl cellulose (11%) Microcrystalline cellulose (89%)	50.0 mg
Sucrose	1.75 g
Sodium benzoate	10.0 mg
Flavor and Color	q.v.
Purified water to	5.0 mL

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Formulation Example 8

Ingredient	Quantity (mg/capsule)
Active Ingredient	15.0 mg
Starch	407.0 mg
Magnesium stearate	3.0 mg
Total	425.0 mg

The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425.0 mg quantities.

Formulation Example 9

A formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	5.0 mg
Corn Oil	1.0 mL

Formulation Example 10

A topical formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	1-10 g
Emulsifying Wax	30 g
Liquid Paraffin	20 g
White Soft Paraffin	to 100 g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable

delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent 5,011,472, which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

Other suitable formulations for use in the present invention can be found in *Remington's Pharmaceutical Sciences*, Mace Publishing Company, Philadelphia, PA, 17th Ed (1985).

Utility

The multibinding agents of the present invention are useful for modulating the PPARγ receptor, and, depending on the composition of the multibinding agent, also the RXR receptor. The modulation of these receptors in preadipocytes promotes gene transcription and differentiation to adipocytes. Further, modulation of these receptor sites leads gene transcription and reduction of blood glucose, serum triglycerides, and serum non-esterified fatty acids. These effects are useful in treating mammalian conditions modulated by the PPARγ receptor, including non-insulin dependent diabetes mellitus, cancer, hyperlipedemia, arteriosclerosis and inflammatory diseases, for example.

In order to further illustrate the present invention and advantages thereof, the following specific examples are given but are not meant to limit the scope of the claims in any way.

EXAMPLES

In the Preparations and Examples below, all temperatures are in degrees Celsius (unless otherwise indicated) and all percentages are weight percentages (also unless otherwise indicated).

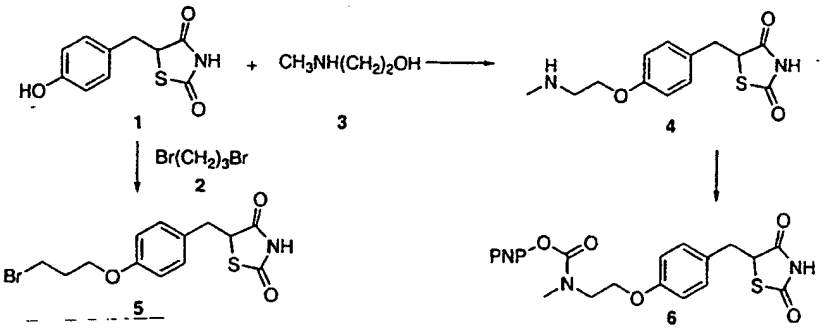
Preparations 1-22 and Examples1-14 are given as representative examples of methods for preparing compounds of this invention.

In the Procedures and Examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

Å	=	Angstroms
cm	=	centimeter
DIC	=	2-dimethylaminoisopropyl chloride hydrochloride
DCC	=	*N,N*-dicyclohexylcarbodiimide
DCM	=	dichloromethane
DIPEA	=	diisopropylethylamine
DMA	=	*N,N*-dimethylacetamide
DMAP	=	*4-N,N*-dimethylaminopyridine
DMF	=	*N,N*-dimethylformamide
DMSO	=	dimethylsulfoxide
DPPA	=	diphenylphosphoryl azide
g	=	gram
HBTU	=	1-hydroxybenzotrizole
HPLC	=	high performance liquid chromatography
mg	=	milligram
MIC	=	minimum inhibitory concentration
min	=	minute
mL	=	milliliter

	mm	=	millimeter
	mmol	=	millimol
	N	=	normal
	PyBOP	=	pyridine benzotriazol-1-yloxy-tris(dimethyl-amino)phosphonium hexafluorophosphate
	t-BOC	=	*tert*-butyloxycarbonyl
	TBAF	=	tetrabutyl ammonium fluoride
	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran
	tlc	=	thin layer chromatography
	μL	=	microliters

Preparation 1: 5-[4-(2-methylaminoethoxy)phenyl]methyl-2,4-thiazolidinedione, 4, 5-[4-(3-bromopropyloxy)phenyl]methyl-2,4-thiazolidinedione, 5 and 5-[4-[2-(4-nitrophenylcarbamoylmethylamino)ethoxylphenyl]methyl-2,4-thiazolidinedione, 6.



A. 5-[(4-Hydroxyphenyl)methyl]-2,4-thiazolidinedione 1, prepared as described in Chem. Pharm. Bull., 1982,30, 3580, (5 mmol) is dissolved in THF (50 mL), and arid triphenylphosphine (7.5 mmol) and 2-methylaminoethanol 3 (3 mmol) are added. A solution of diethyl azodicarboxylate (7.5 mmol) in THF (15 mL) is added over 30 minutes. The progress of the reaction is monitored by tlc. When it is complete, the solution is added to water and extracted with CH_2Cl_2. The organic phase is washed, dried and evaporated, and the residue is chromatographed to afford the compound 4.

B. Using the above procedure, but using different aminoalcohols in place of 3,

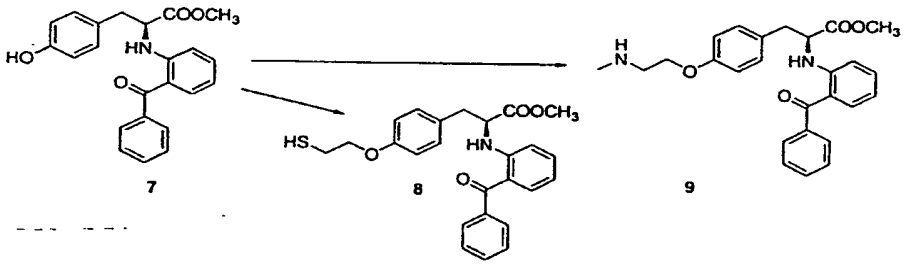
compounds corresponding to 4 may be obtained.

C. 5-[(4-Hydroxyphenyl)methyl]-2,4-thiazolidinedione 1 (5 mmol) is dissolved in DMF (50 mL), 1,3-dibromopropane 2 (2.5 mol), K_2CO_3 (1 g) and KI (50 mg) are added. The mixture is heated at 70°. The progress of the reaction is monitored by tlc. When it is complete, the solution is added to water and extracted with CH_2Cl_2. The organic phase is washed, dried and evaporated, and the residue is chromatographed to afford the compound 5.

D. Using the above procedure, but using different dibromides in place of 2, compounds corresponding to 5 may be obtained.

E. The compound 4 (1 mmol) is dissolved in THP (25 mL), and pyridine (2 mmol) and p-nitrophenylchloroformate (1.25 mmol) are added. After 1 hour the solvents are removed under vacuum to afford the compound 6.

Preparation 2: (2S) Methyl 2-[(2-benzoylphenyl)amino]-3-[4-(2-methylamino)ethoxyphenyl] propionate, 9, and (2S) methyl 2-(2-benzoylphenyl)amino-3-14-(2-mercaptoethoxy)phenyl] propionate 8.



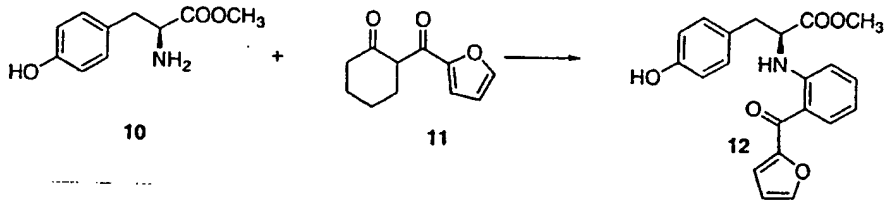
A. Using the alkylation conditions of Preparation 1C, (2S) methyl 2-(2-benzoylphenyl)amino-3-(4-hydroxyphenyl) propionate 7, prepared as described in J. Med. Chem., 1998, 41, 5020, is reacted with 2-bromoethanethiol to afford the compound 8,

B. Using the Mitsonobu reaction conditions of Preparation 1A, (2S) methyl 2-(2-benzoylphenyl)amino-3-(4-hydroxyphenyl) propionate, 7, prepared as described in J. Med. Chem., 1998, 41, 5020, is reacted with 2-

methylaminoethanol 3, to afford the compound 9.

C. Using the above procedures, but employing different bromoalkyl mercaptans or aminoalcohols in place of 2-bromoethanethiol or 2-methylaminoethanol 3, the compounds corresponding to 8 or 9 are obtained.

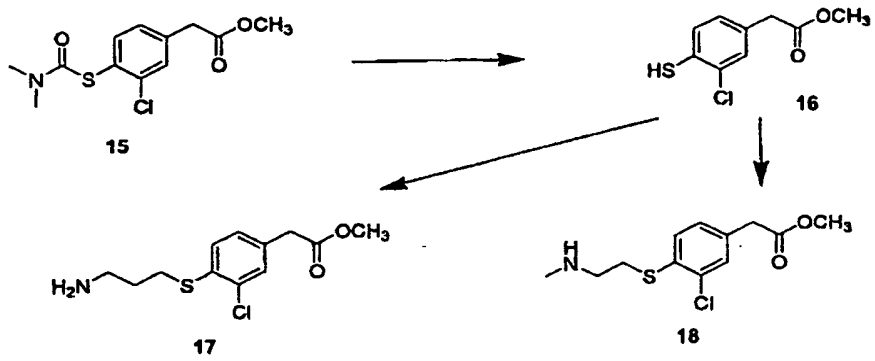
Preparation 3: (2S) methyl 2-(2-furoylphenyl)amino-3-(4-hydroxyphenyl) propionate, 12.



A. 2-Furoylcyclohexanone, 11, prepared as described in Gazz. Chim. Ital., 1987, 117, 645, (5 mmol) is dissolved in anisole (50 mL) and 1-tyrosine methyl ester 10, (5 mmol) and 10 % Pd/C (2 g) are added. The mixture is heated under reflux. After 4 hours, the cooled solution is filtered. The solvent is removed under vacuum and the residue is chromatographed to afford the compound 12.

B. Using the above procedure, but employing in place of 2-furylcylcohexanone different 2-aroylcyclohexanones, compounds analogous to 12 may be obtained.

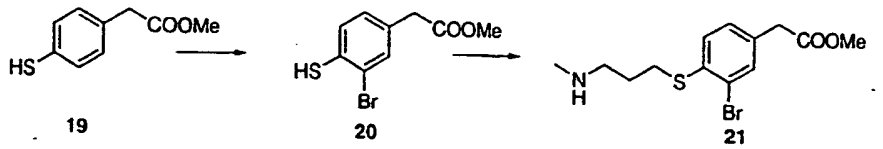
Preparation 4: methyl 4-(3-aminopropylthio)-3-chlorophenyl acetate, 17, and methyl 4-(2-methylaminoethylthio)-3-chlorophenyl acetate, 18.



A. 3-chloro-4-dimethylaminocarbamoylthiophenylacetic acid methyl ester 15 (US Patent 5,859,051) (100 mmol) is dissolved in 250 mL of MeOH and added to a 0.5M solution (100 mmol, 200 mL) of sodium methoxide and heated to 70°C for 2 h. The reaction is cooled to room temperature, neutralized with 1N HCl, and diluted with ether (2000 mL). The organic layer was separated, washed with brine, and dried over $MgSO_4$, filtered and evaporated. The crude methyl 3-chloro-4-thiophenylacetate 16 is utilized without further purification.

B. Using the Mitsonobu procedure of Preparation 1A, the mercaptan 16 is reacted respectively with 3-aminopropanol and 2-(methylamino)ethanol to afford the compounds 17 and 18 respectively.

Preparation 5: methyl 3-bromo-4-[(3-methylaminopropyl)mercaptolphenylacetate, 21.

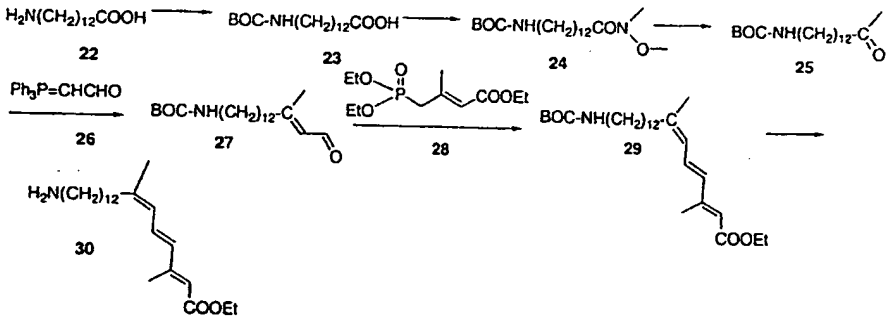


A. Methyl 4-mercaptophenyl acetate 19, (5 mmol) is dissolved in AcOH (50 mL). Bromine (5 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the solution is added to water and extracted with EtOAc. The organic phase is washed, dried and evaporated, and the residue is chromatographed to afford methyl 3-bromo-4-mercaptophenyl acetate 20.

B. Using the conditions of Preparation 1C, the above compound 20 is reacted with 3-(methylamino)propyl bromide to afford the compound 21.

C. Using the above procedure, but employing in place of 3-(methylamino)propyl bromide, different aminoalkyl bromides, compounds corresponding to 21 may be obtained.

Preparation 6: ethyl 19-amino-3,7-dimethylnonadeca-2(E),4(E),6(E)-trienoate, 30.



A. 13-Aminotridecanoic acid 22 (5 mmol) is dissolved in 1N NaOH (20 mL) and water (80 mL). To the solution is added $(BOC)_2O$ (10 mmol) in portions. After 1 hour, the solution is acidified with dilute HCl, and is extracted with EtOAc. The extract is dried and evaporated, and the residue is chromatographed to afford 13-(tert-butoxycarbonylamino)tridecanoic acid 23.

B. The above compound 23 (3 mmol) is dissolved in DMF (50 mL) and N,O-dimethylhydroxylamine (4 mmol) and dicyclohexylcarbodiimide (DCC) (3 mmol) are added. The progress of the reaction is monitored by tlc. When

it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford 13-(tert-butoxycarbonylamino)-N,O-dimethyltridecanoylhydroxylamine, 24.

C. The above compound 24 (2 mmol) is dissolved in ether (50 mL) and the solution is cooled to -80°. A solution of 1M methyl lithium in hexane (3 mL) is added. After 1 hour water (1 mL) is added. The ethereal solution is dried and evaporated, and the residue is chromatographed to afford 14-(tert-butoxycarbonylamino)tetradecan-2-one, 25.

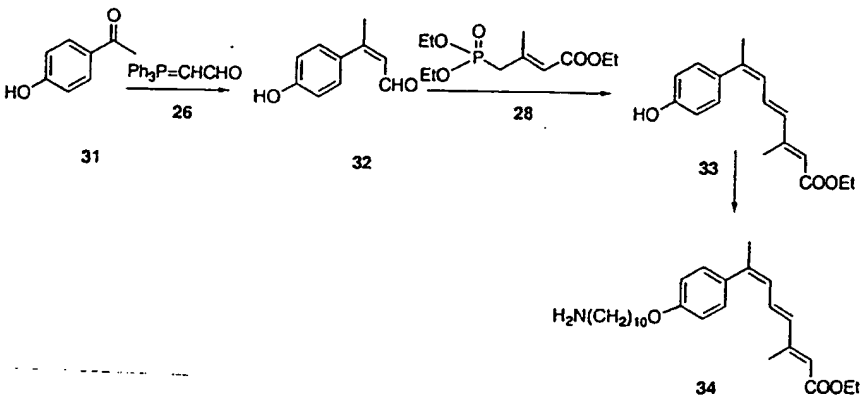
D. The ketone 25 (2 mmol) is dissolved in MeCN (25 mL) and (triphenylphosphoranylidene)acetaldehyde 26 (2 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford 15-(tert-butoxycarbonylamino)-3-methylpentadeca-2(E)-enealdehyde, 27.

E. Ethyl 4-(diethoxyphosphinyl)-2(E)-butenoate 28, prepared as described in US Patent 5,770,383, (2 mmol) is dissolved in THF (25 mL) and 50 % NaH in oil (2 mmol) is added. After 1 hour, the aldehyde 27 (2 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford ethyl 19-(tert-butoxycarbonylamino)-3,7-dimethylnonadeca-2(E),4(E),6(E)-trienoate, 29.

F. The above compound 29 (1 mmol) is dissolved in 1N HCl in EtOH (20 mL). After 1 hour, the solvent is removed under vacuum and the residue is chromatographed to afford the compound 30.

G. Using the above procedures, but employing in Step A different 1,n-amino acids in place of 13-aminotridecanoic acid, there may be obtained corresponding compounds analogous to 30.

Preparation 7: ethyl 3,7-dimethyl-7-[4-(12-aminodecyloxy)phenyl]hepta-2(E),4(E),6(E)-trienoate, 34.



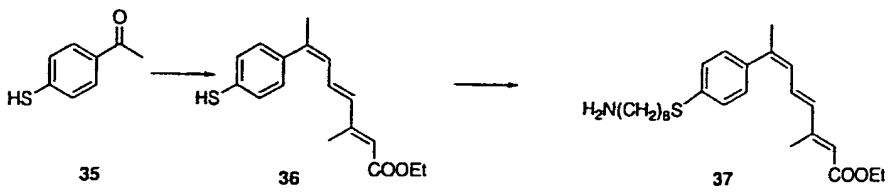
A. Using the procedure of Preparation 6D, 4-hydroxyacetophenone 31 is reacted with (triphenylphosphoranylidene)acetaldehyde 26 to afford 3-(4-hydroxyphenyl)but-2(E)-enal, 32.

B. Using the procedure of Preparation 2E, the sodium salt of the aldehyde 32 is reacted with ethyl 4-(diethoxyphosphinyl)-2(E)-butenoate 28 to afford ethyl 3,7-dimethyl-7-(4-hydroxyphenyl)hepta-2(E),4(E),6(E)-trienoate, 33,

C. The above compound 33 (1 mmol) is dissolved in DMF (15 mL), and 10-amino-1-bromodecane (1 mmol), K_2CO_3 (0.5 g) and KI (50 mg) are added. The mixture is heated at 60° and the progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford the compound 34.

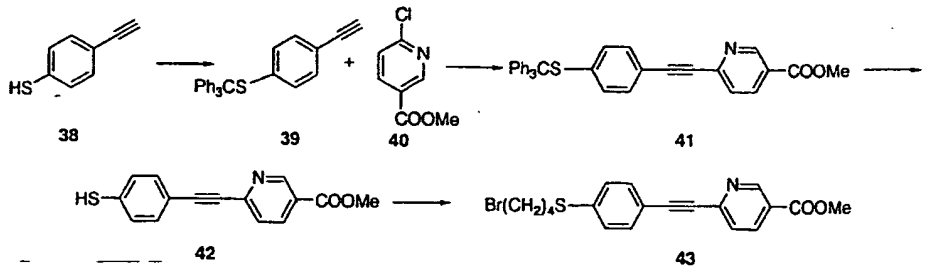
D. Using the above procedure, but employing in Step C different 1,n-aminoalkyl bromides in place of 10-amino-1-bromodecane, compounds analogous to 34 may be obtained.

Preparation 8: ethyl 3,7-dimethyl-7-[4-(8-aminooctylthio)phenyl]hepta-2(E),4(E),6(E)-trienoate, 37.



Using the procedures of Preparation 7, and employing in Step A 4-mercaptoacetophenone 35 (prepared as described in WO 9842758) in the place of 4-hydroxyacetophenone, and employing in Step C 8-aminooctyl bromide in the place of 10-aminodecyl bromide in Step C, 35 is converted through intermediate 36 to the desired compound 37.

Preparation 9: methyl 2-[4-(4-bromobutylthio)phenylethynyl]pyridine-5-carboxylate, 43.



A. 4-Mercaptophenylacetylene 38, prepared as described in Liebigs Ann., 1996, 2107, (5 mmol) is dissolved in pyridine (25 mL) and triphenylmethyl chloride (5 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford 4- (triphenylmethylthio)phenylacetylene, 39.

B. $(Ph_3P)_2PdCl_2$ (0.3 g) is added to dry THF (50 mL) under an inert atmosphere, and CuI (75 mg) is added. After 10 minutes, Et_3N (3 mL) and

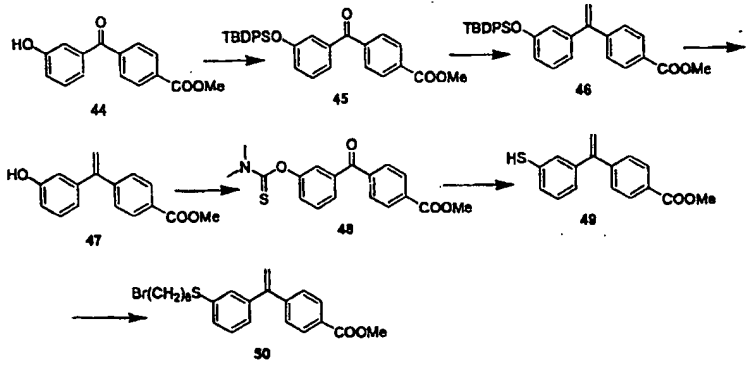
the acetylene 39 (20 mmol) are added, and after a further 10 minutes, methyl 2-chloropyridine-5-carboxylate 40, prepared as described in US Patent 5,693,611, (20 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford methyl 2-[4(triphenylmethylthio)phenylethynyl]pyridine-5-carboxylate, 41.

C. The above compound 41 (5 mmol) is dissolved in a 1M solution of HCl in AcOH (25 mL). The mixture is heated at 60° and the progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford methyl 2-[4-mercaptophenylethynyl]pyridine-5-carboxylate, 42.

D. Using the conditions of Preparation 7C, the compound 42 is reacted with one molar equivalent of 1,4-dibromobutane to afford the compound 43.

E. Using the above procedure, but employing in Step D different 1,n-dibromoalkanes in place of 1,4-dibromobutane, compounds analogous to 43 may be obtained.

Preparation 10: 1-[3-(6-bromohexylthio)phenyl]-1-[4-carbomethoxyphenyl]ethylene, 50.



A. Methyl 3'-hydroxybenzophenone-4-carboxylate 44, prepared as described in Macromol. Chem. Phys., 1997, 198, 2599, (10 mmol) is dissolved in THF (100 mL) and tert-butylchlorodiphenylsilane (10 mmol) and imidazole (10 mmol) are added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford methyl 3'-(tert-butyldiphenylsilyloxy)benzophenone-4-carboxylate, 45.

B. Methyl triphenylphosphonium bromide (10 mmol) is suspended in THF (50 mL) and 1M BuLi in hexane (10 mL) is added. After 15 minutes, a solution of the compound 45 (10 mmol) in THF (25 mL) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford 1-[3-(tert-butyldiphenylsilyloxy)phenyl]-1-[4-carbomethoxyphenyl]ethylene 46.

C. The above compound 46 (5 mmol) is dissolved in THF (50 mL) and Bu_4NF (6 mmol) in THF is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford 1-[3-hydroxyphenyl]-1-[4-carbomethoxyphenyl]ethylene, 47.

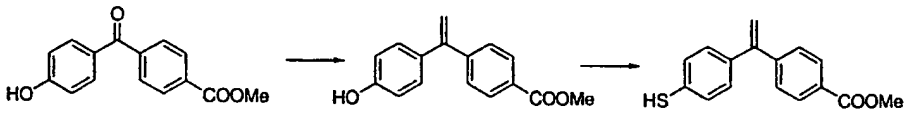
D. The above compound 47 (3 mmol) is dissolved in pyridine (25 mL) and dimethylthiocarbamoyl chloride (4 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford 1-[3-(dimethylthiocarbamoyloxy)phenyl]-1-[4-carbomethoxyphenyl]ethylene, 48. This compound (1 mmol) is dissolved in diphenyl ether (10 mL) and the solution is heated at 250°. The progress of the reaction is monitored by

tlc. When it is complete, the solvent is removed under vacuum. The residue is dissolved in MeOH (20 mL) containing NaOH (1 mmol). The mixture is heated at reflux. The progress of the reaction is monitored by tlc. When it is complete, the solution is acidified with dilute HCl, and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford 1-(3-mercaptophenyl-1-(4-carbomethoxyphenyl)ethylene, 49.

E. Using the procedure of Preparation 9D, the compound 49 is reacted with one molar equivalent of 1,6-dibromohexane to afford the compound 50.

F. Using the above procedure, but employing different 1,n-dibromoalkanes in place of 1,6-dibromohexane, compounds analogous to 50 may be obtained.

Preparation 11: 1-(4-carbomethoxyphenyl)-1-(4-hydroxyphenyl)ethylene, 52 and 1-(4-carbomethoxyphenyl)-1-(4-mercaptophenyl)ethylene 53.

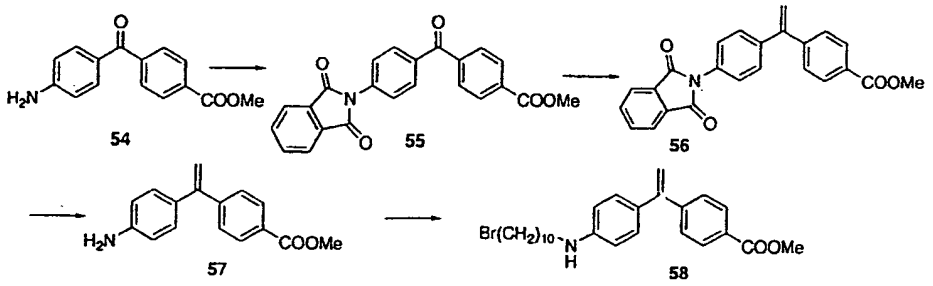


51 52 53

A. Using the procedures of Preparation 10A-C, methyl 4'-hydroxybenzophenone-4-carboxylate 51, prepared as described in J. Med. Chem., 1995, 38, 13, is converted into the compound 52.

B. Using the procedure of Preparation 10D, the phenolic compound 52 is converted into the corresponding thiol 53.

Preparation 12: 1-[4-(10-bromodecylamino)phenyl]-1-(4-carbomethoxyphenyl)ethylene, 58.



A. Methyl 4'-aminobenzophenone-4-carboxylate 54, prepared as described in Uch. Zap. Tekbnol. Inst., 1972, 22, 44, (10 mmol) is dissolved in pyridine (50 mL) and phthalic anhydride (10 mmol) is added. The mixture is heated at 50° and the progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford methyl 4'-(N-phthalimido)benzophenone-4-carboxylate 55.

B. Using the Wittig reaction procedure of Preparation 10B, the compound 55 is converted into 1-(4-carbomethoxyphenyl)-1-[4-(N-phthalimido)phenyl]ethylene.

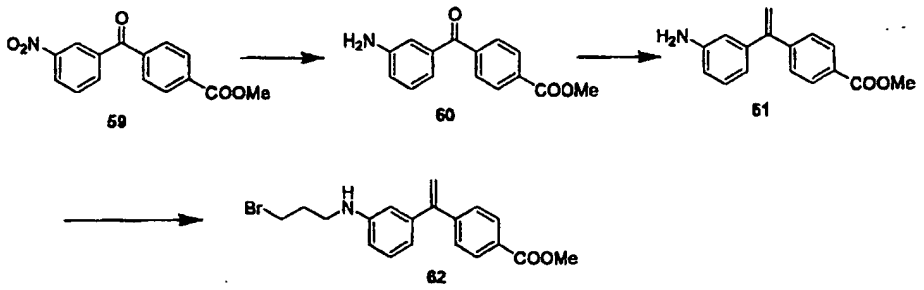
C. The compound 56 (5 mmol) is dissolved in MeOH (50 mL) and 85% hydrazine hydrate (5 mL) is added. The solution is heated at reflux. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to dilute HCl and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford 1-(4-aminophenyl)-1-(4-catbomethoxyphenyl)ethylene, 57.

D. Using the alkylation procedure of Preparation 7C, the compound 57 is reacted with one molar equivalent of 1,10-dibromodecane, to afford the compound 58.

E. Using the above procedure, but employing different 1,n-dibromoalkanes in

place of 1,10-dibromodecane, compounds analogous to 58 may be obtained.

Preparation 13: 1-[3-(3-bromopropylamino)phenyl]-1-(4-carbomethoxyphenyl)ethylene, 62.



A. 4-carbomethoxy-3'-nitrobenzophenone, 59 prepared as described in Japanese Patent 51225013, (10 mmol) is dissolved in MeOH (50 mL) and $SnCl_2$ dihydrate (40 mmol) is added. The mixture is heated at reflux. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to dilute HCl and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford 3'-amino-4-carbomethoxybenzophenone, 60.

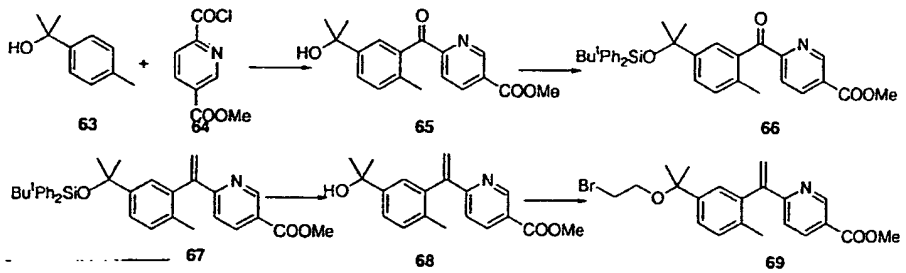
B. Using the procedure of Preparation 12A, the compound 60 is reacted with phthalic anhydride to afford 4-carbomethoxy-3'-(N-phthalimido)benzophenone. The latter compound is reacted with methylenetriphenylphosphorane, using the procedure of Preparation 10B, to afford 1-(4-carbomethoxyphenyl)-1-[(3'-N-phthalimido)phenyl]ethylene. Using the procedure of Preparation 12C, the latter compound is reacted with hydrazine to afford 1-(3-aminophenyl)-1-(4-carbomethoxyphenyl)ethylene, 61.

C. Using the alkylation procedure of Preparation 7C, the compound 61 is reacted with 1.0 molar equivalents of 1,3-dibromopropane to afford the

compound 62.

D. Using the above procedure, but employing different 1,n-dibromoalkanes in place of 1,3-dibromopropane, compounds analogous to 62 may be obtained.

Preparation 14: 1-(5-carbomethoxy-2-pyridyl)-1-[3-(4-bromo-2-methyl-3-oxa-2-pentyl)-6-methylphenyl]ethylene, 69.



A. $AlCl_3$ (5 mmol) and nitromethane (5 mmol) are stirred in dry CH_2Cl_2 at O°C until clear solution is obtained. p-Cymene-8-ol 63 (5 mmol) and 2-chlorocarbonyl-5-carbomethoxypyridine 64, prepared as described in J. Med. Chem., 1995, 38, 3146, (5 mmol) are added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford 5-carbomethoxy-2-[3-(1-hydroxy-1-methylethyl)-6-methylbenzoyl]pyridine, 65.

B. Using the silylation procedure of Preparation 10A, the compound 65 is converted into 5-carbomethoxy-2-[3-(1-tert-butyldiphenylsilyloxy-1-methylethyl)-6-methylbenzoyl]pyridine, 66.

C. Using the Wittig reaction procedure of Preparation 10B, the compound 66 is converted into 1-[3-(1-tert-butyldiphenylsilyloxy-1-methylethyl)-6-methylphenyl]-1-(5-carbomethoxy-2-pyridyl)ethylene, 67.

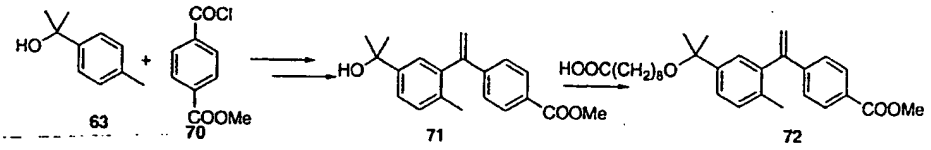
D. Using the desilylation procedure of Preparation 10C, the compound 67 is converted into 1-[3-(1-hydroxy-1-methylethyl)-6-methylphenyl]-1-(5-

carbomethoxy-2-pyridyl)ethylene, 68.

E. The above compound 68 (1 mmol) is dissolved in DMF (10 mL) and 50 % NaH in oil (1 mmol) is added. When hydrogen evolution has ceased, 1,2-dibromoethane (1 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford the compound 69.

F. Using the above procedure, but employing different 1,n-dibromoalkanes in place of 1,2-dibromoethylene, compounds analogous to 69 may be obtained.

Preparation 15: 1-[3-(11-carboxy-2-methyl-3-oxa-2-undecyl)phenyl]-1-(4. carbomethoxyphenyl)ethylene, 72.



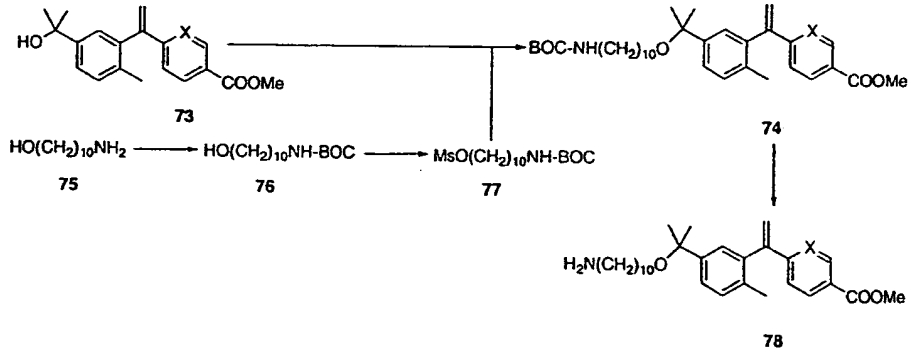
A. Using the procedures of Preparation 14A-D, and employing in Step A methyl 4-chlorocarbonylbenzoate 70 in place of 2-chlorocarbonyl-5-carbomethoxypyridine 64, p-cymene-8-ol 63 is converted into 1-[3-(1-hydroxyl-methylethyl)-6-methylphenyl)-1-(4-carbomethoxyphenyl)ethylene, 71.

B. The above compound 71 (5 mmol) is dissolved in DMF (50 mL) and 50 % NaH in oil (5 mmol) is added. When hydrogen evolution has ceased, tert-butyl 8-bromooctanoate (5 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to dilute HCl and extracted with EtOAc. The extract is dried and evaporated and the residue is dissolved in TFA (50 mL). After 1 hour, the solvent is removed under vacuum, and the residue is chromatographed to afford the compound

72.

C. Using the above procedure, but employing different tert-butyl bromoalkanoates in place of tert-butyl 8-bromooctanoate, the compounds analogous to 72 are obtained.

Preparation 16: 1-[3-(13-amino-2-methyl-3-oxa-2-tridecanyl)-6-methylphenyl)-1-(4-carbomethoxyphenyl)ethylene 78, in which X is CH, and 1-[3-(13-amino-2-methyl-3-oxa-2-tridecanyl)-6-methylphenyl)-1-(5-carbomethoxy-2-pyridyl)ethylene, 78, in which X is N.



A. 10-Aminodecanol (20 mmol) is dissolved in CH_2Cl_2 (100 mL) and Et_3N (25 mmol) and BOC-ON (Aldrich Chemical Company) (20 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to dilute HCl and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford 10-(tert-butoxyoarbonylamino)decanol 76.

B. The above compound 76 (5 mmol) is dissolved in CH_2Cl_2 (50 mL) and pyridine (5 mmol) and methanesulfonyl chloride (5 mmol) are added. After 1 hour the solution is washed with dilute HCl, and dried and evaporated to afford 10-(tert-butoxycarbonylamino)-1-(methanesulfonyloxy)decanol 77.

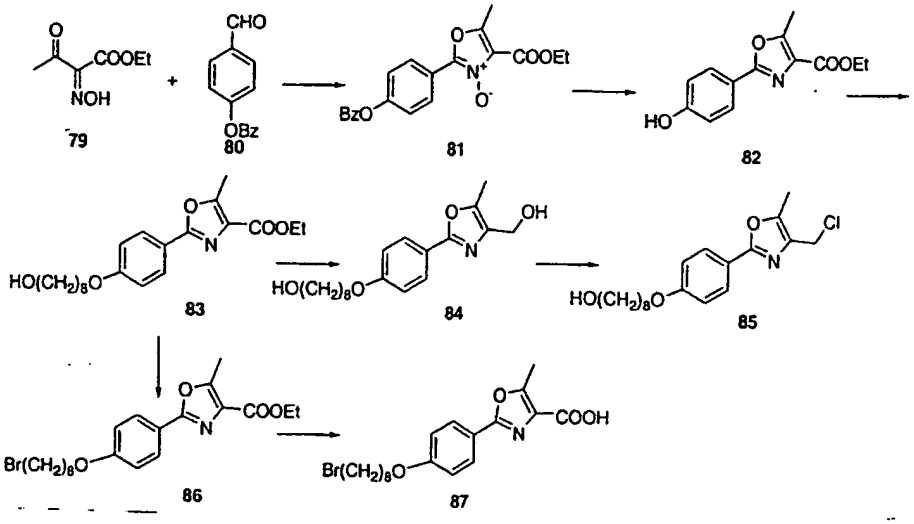
C. 5-Carbomethoxy-2-[3-(1-hydroxy-1-methylethyl)-6-methylbenzoyllpyridine,

65 (2 mmol) is dissolved in DMF (25 mL) and 50% NaH in oil (2 mmol) is added. When hydrogen evolution has ceased, 10-(tert-butoxycarbonylamino)-1-(methanesulfonyloxy)decanol 77 (2 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford 1-[3-(13-tert-butoxycarbonylamino-2-methyl-3-oxa-2-tridecanyl)-6-methylphenyl)-1-(5-carbomethoxy-2-pyridyl)ethylene 74, in which X is N.

D. Using the deprotection procedure of Preparation 6F, the above compound 74 is converted into the compound 78 in which X is N.

E. Using the procedures C and D above, but employing in Step C 1-[3-(1-hydroxymethylethyl)-6-methylphenyl)-1-(4-carbomethoxyphenyl)ethylene, 71 in place of 5-carbomethoxy-2-[3-(1-hydroxy-1-methylethyl)-6-methylbenzoyl]pyridine, 65, there is obtained the compound 78 in which X is CH.

Preparation 17: 4-chloromethyl-5-methyl-2-[4-(8-hydroxyoctyloxy)phenyl]oxazole 85, and 2-[4-(8-bromooctyloxy)phenyl]-5-methyloxazole-4-carboxylic acid 87.



A. Ethyl 2-(hydroxyimino)-3-oxobutyrate 79, prepared as described in J. Am. Chem. Soc., 1938, 60, 1328, (0.5 mol) and 4-benzyloxybenzaldehyde 80 (0.6 mol) are dissolved in AcOH (200 mL) and the solution is cooled to 0°C. Dry HCl gas is passed in for 2 hours, and then ether (600 mL) is added. The mixture is filtered to afford ethyl 2-[(4-benzyloxy)phenyl]-5-methyl-3-oxooxazole-4-carboxylate, 81.

B. The above compound 81 (0.1 mol) is dissolved in EtOH (200 mL) and 10% Pd/C (2 g) is added. The mixture is hydrogenated in a Parr shaker at 50 psi. The progress of the reaction is monitored by tlc. When it is complete, the solution is filtered and the solvent is removed under vacuum. The residue is chromatographed to afford ethyl 2-(4-hydroxyphenyl)-5-methyloxazole-4-carboxylate 82.

C. The above compound 82 (50 mmol) is dissolved in DMF (50 mL). 8-bromooctanol (50 mmol), K_2CO_2 (5 g) and KI (100 mg) are added. The mixture is heated at 70° and the progress of the reaction is monitored by tlc. When it is complete, the cooled solution is added to water and extracted with EtOAc. The extract is dried and evaporated to afford ethyl 2-(4-(8-hydroxyoctyl)phenyl]-5-methyloxazole-4-carboxylate 83.

D. The above compound 83 (50 mmol) is dissolved in ether (75 mL) and the solution is added over a period of 30 minutes to a suspension of LAH (2 g) in ether (50 mL) at 0-10°C. After 1 hour, the mixture is diluted with THF (50 mL). Water is added cautiously to destroy excess LAH. AcOH (10 mL) is added, and the solution is filtered and evaporated. The residue is chromatographed to afford 4-hydroxymethyl-2-[4-(8-hydroxyoctyl)phenyl]-5-methyloxazole, 94.

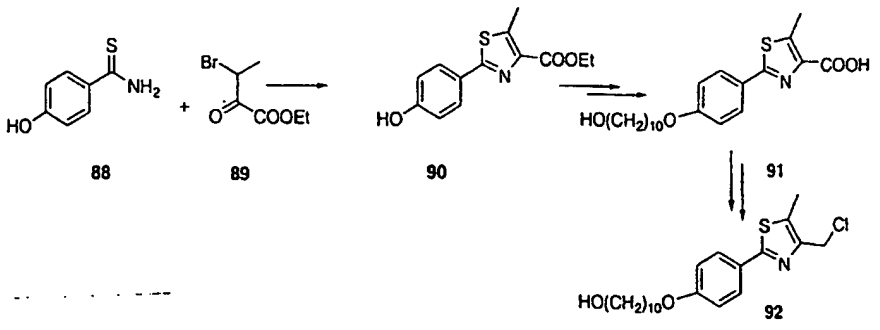
E. Using the above procedure, but employing in Step C, in place of 8-bromooctanol, different bromoalkanols, compounds corresponding to 84 may be obtained.

F. The compound 84 (50 mmol) is dissolved in ether (100 mL) and PPh_3 (75 mmol) and CCl_4 (75 mmol) are added. The progress of the reaction is monitored by tlc. When it is complete, the solution is added to water. The organic phase is dried and evaporated to afford 4-chloromethyl-2-[4-(8-hydroxyoctyl)phenyl]-5-methyloxazole 85.

G. The compound 83 (50 mmol) is dissolved in CH_2Cl_2 (100 mL) and CBr_4 (60 mmol) and PPN (60 mmol) are added. The progress of the reaction is monitored by tlc. When it is complete, the solution is added to water. The organic phase is dried and evaporated and the residue is chromatographed to afford ethyl 2-[4-(8-bromooctyl)phenyl]-5-niethyloxazole-4-carboxylate, 86.

H. The compound 86 (30 mmol) is dissolved in THF (20 mL) and a solution of $LiOH,H_2O$ (35 mmol) in water (20 mL) is added. The progress of the reaction is monitored by tlc. When it is complete, the solution is added to dilute HCl. The aqueous solution is extracted with EtOAc. The organic phase is dried and evaporated and the residue is chromatographed to afford the compound 87.

Preparation 18: 2-[4-(10-hydroxydecyloxy)phenyl]-5-methylthiazole-4-carboxylic acid, 91, and 4-chloromethyl-2,[4-(10-hydroxydecyloxy)phenyl]-5-methylthiazole, 92.

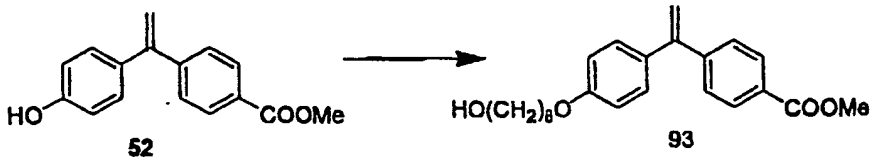


A. 4-Hydroxyphenylthiourea, 88, prepared as described in Tetrahedron, 1989, 45, 4519, (50 mmol) and ethyl 3-bromo-2-oxobutyrate 89 (50 mmol) are heated at reflux in MeCN (100 mL). The progress of the reaction is monitored by tlc. When it is complete, the cooled solution is added to water and extracted with EtOAc. The organic phase is dried and evaporated and the residue is chromatographed to afford ethyl 2-(4-hydroxyphenyl)-5-methylthiaxole-4-carboxylate, 90.

B. Using the alkylation procedure of Preparation 17C, the compound 90 is reacted with 10-bromodecanol to afford ethyl 2-(4-(10-hydroxydecyloxy)phenyl]-5-methylthiazole-4-carboxylate. Using the hydrolysis procedure of Preparation 10H, the latter compound is converted into the carboxylic acid compound 91.

C. Using the reduction procedure of Preparation 17D, followed by the chlorination procedure of Preparation 10F, 2-[4-(10-hydroxydecyloxy)phenyl]-5-methylthiazole-4-carboxylic acid 91 is converted into the compound 92.

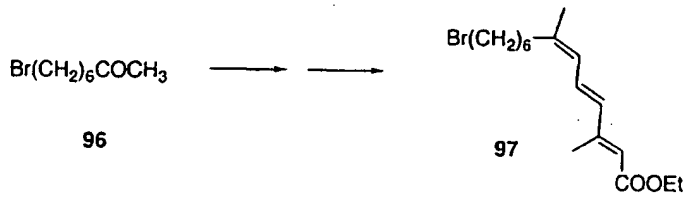
Preparation 19: 1-(4-carbomethoxyphenyl)-1-[4-(8-hydroxyoctyloxy)phenyl] ethylene 93.



1-(4-carbomethoxyphenyl)-1-(4-hydroxyphenyl)ethylene, 52, (50 mmol) is dissolved in DMF (50 mL). 8-bromooctanol (50 mmol), K_2CO_3 (5 g) and KI (100 mg) are added. The mixture is heated at 70° and the progress of the reaction is monitored by tlc. When it is complete, the cooled solution is added to water and extracted with EtOAc. The extract is dried and evaporated to afford 1-(4-

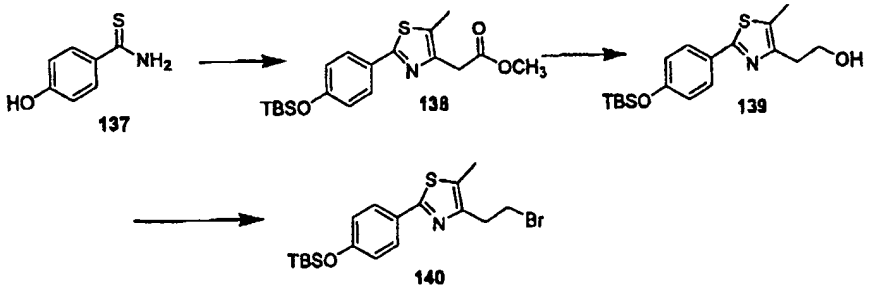
carbomethoxyphenyl)-1-[4-(8-hydroxy-octyloxy)phenyl]ethylene, 93.

Preparation 20: ethyl 13-bromo-3,7-dimethyltrideca-2(E),4(E),6(E)-trienoate, 97.



Using the procedures of Preparation 6D and 6E, 8-bromooctan-2-one 96, prepared as described in J. Chem. Res. Synop., 1993, 249, is converted into the compound 97.

Preparation 21: 2-[2-(4-tert-butyldimethylsilyloxyphenyl)-5-methylthiazol-4-yl]ethanol 139 and 2-[2-(4-tert-butyldimethylsilyloxyphenyl)-5-methylthiazol-4-yl]ethyl bromide 140.



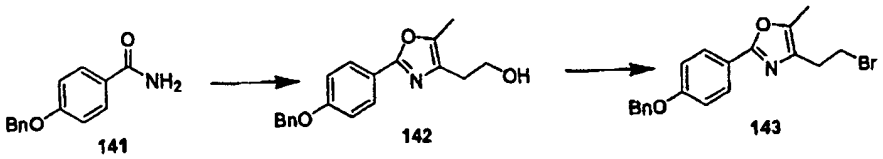
A. Using the procedures described in J. Med. Chem 1998, 41, (25), 5037-5054 for the preparation of 2-[2-(4-fluorophenyl)-5-methyloxazol-4-yl]-ethanol from 4-fluorobenzamide, 4-hydroxythiobenzamide 137 (Helv, Chim. Acta. 16, 1933; 999, 1007) is converted to 2-[2-(4-hydroxyphenyl)-5-methyloxazol-4-yl]-acetic acid methyl ester. The ester (150 mmol) is dissolved in THF (500 mL) and tert-butylchlorodimethylsilane (150 mmol) and imidazole (150 mmol) are added. The progress of the reaction is

monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford 138.

B. Compound 138 (120 mmol) is dissolved in 1L of THF under nitrogen at 0°C and 120 mL of a 1M solution of LAH in THF is added over 15 min. The reaction is allowed to stir at room temperature for 2 h and then is cooled to 0°C. Slowly 5 mL of water is added, followed by 10 mL of 15 % NaOH, and reaction is stirred vigorously for 20 min. before filtering. The filtrate is dried, filtered and concentrated in vacuo. The crude is chromatographed on silica get to yield 2-[2-(4-tert-butyldimethylsilyloxyphenyl)-5-methylthiazol-4-yl]-ethanol 139.

C. The alcohol 139 (50 mmol) is dissolved in CH_2Cl_2 (100 ML) and CBr_4 (60 mmol) and PPh_3 (60 mmol) are added. The progress of the reaction is monitored by tlc. When it is complete, the solution is added to water, shaken and separated. The organic phase is dried and evaporated and the residue is chromatographed to afford 2-[2-(4-tert-butyldimethylsilyloxyphenyl)-5-methylthiazol-4-yl]-ethyl bromide 140.

Preparation 22: 2-[2-(4-benzyloxyphenyl)-5-methyloxazol-4-yl]-ethanol 142 and 2(2-(4-benzyloxyphenyl)-5-methyloxazol-4-yl]-ethyl bromide 143.

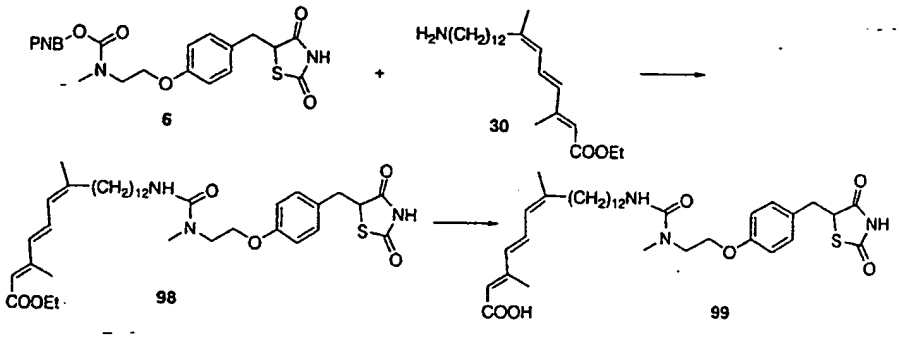


A. Using the procedures described in J. Med. Chem 1998, 41, (25), 5037-5054 for the preparation of 2-[2-(4-fluorophenyl)-5-methyloxazol-4-yl]-ethanol from 4-fluorobenzamide, 4-benzyloxybenzamide 141 (J. Med. Chem.1977, 20, 1388-1393) is converted to 2-[2-(4-benzyloxyphenyl)-5-methyloxazol-4-yl]-acetic acid methyl ester.

B. The ester (120 mmol) is dissolved in 1L of THF under nitrogen at 0°C and 120 mL of a 1M solution of LAH in THF is added over 15 min. The reaction is allowed to stir at room temperature for 2 h and then is cooled to 0°C. Slowly 5 mL of water is added, followed by 10 mL of 15 % NaOH, and reaction is stirred vigorously for 20 min. before filtering. The filtrate is dried over solid Na_2SO_4, filtered and concentrated in vacuo. The crude is chromatographed on silica gel to yield 2-[2-(4-tert-butyldimethylsilyloxyphenyl)-5-methyloxazol-4-yl]-ethanol 142.

C. The alcohol 142 (50 mmol) is dissolved in CH_2Cl_2 (100 mL) and CBr_4 (60 mmol) and PPh_3 (60 mmol) are added. The progress of the reaction is monitored by tlc. When it is complete, the solution is added to water, shaken and separated. The organic phase is dried and evaporated and the residue is chromatographed to afford 2-[2-(4-tert-butyldimethylsilyloxyphenyl)-5-methyloxazol-4-yl]-ethyl bromide 143.

Example 1: Reaction between 5-[4-[2-(4-nitrophenylcarbamoylmethylamino)ethoxy]phenyl]methyl-2,4-thiazolidinedione, 6 and ethyl 19-amino-3,7-dimethylnonadeca-2(E),4(E),6(E)-trienoate, 30 to afford the urea 99.

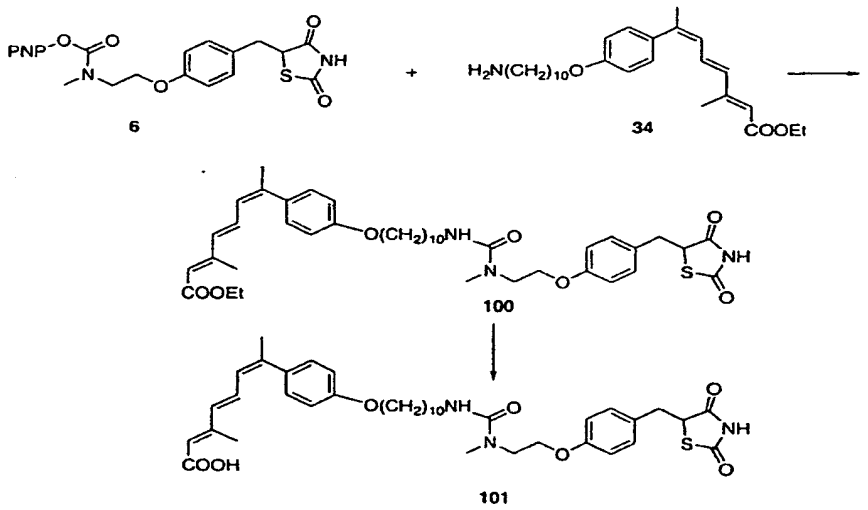


A. The p-nitrophenyl carbamate 6 (1 mmol) and the amine 30 (1 mmol) are dissolved in pyridine (25 mL). The progress of the reaction is monitored by tlc. When it is complete, the mixture is poured into water and extracted

with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the urea 98.

B. The compound 98 (1 mmol) is dissolved in THF (10 mL) and a solution of $LiOH,H_2O$ (l mmol) in water (10 mL) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is poured into dilute HCl and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 99.

Example 2: Reaction between 5-[4-[2-(4-nitrophenylcarbamoylmethylamino)ethoxy]phenyl]methyl-2,4-thiazolidinedione, 6 and ethyl 3,7-dimethyl-7-14-(12-aminodecyloxy)phenyl]hepta-2(E),4(E),6(E)-trienoate, 34 to afford the urea 101.

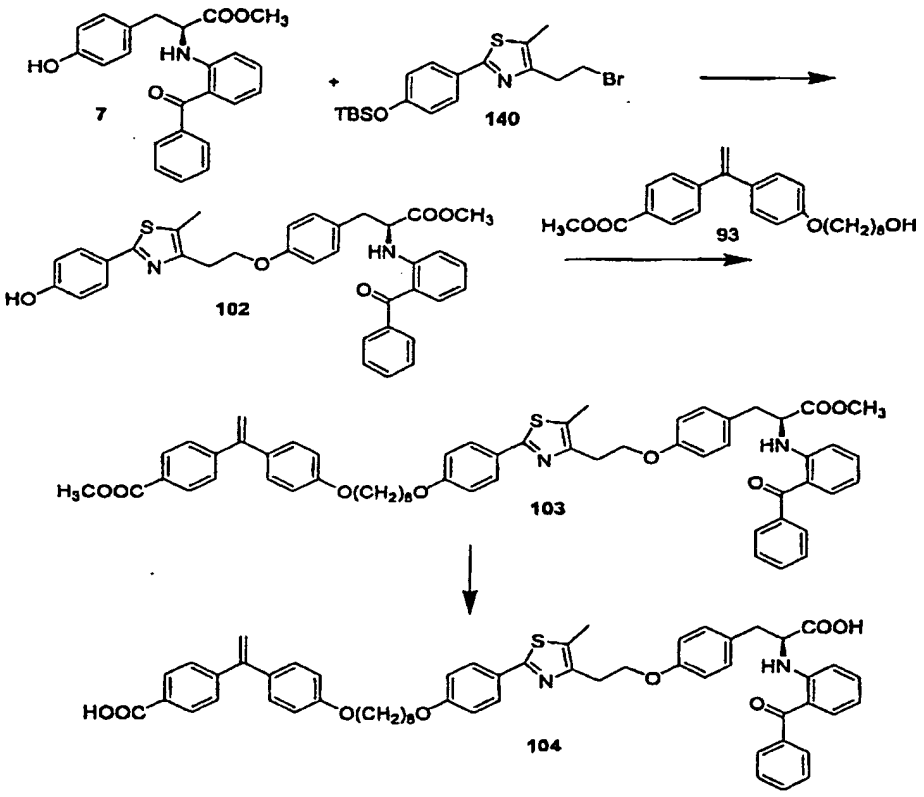


A. Using the procedure of Example 1A, the carbamate 6 and the amine 34 are reacted to produce the urea 100.

B. Using the hydrolysis procedure of Example 1B, the ester 100 is converted into the carboxylic acid 101.

Example 3: Reaction between (2S) methyl 2-(2-benzoylphenyl)amino-3-(4-

hydroxyphenyl) propionate 7, and 2-[2-(4-tert-butyldimethylsilyloxyphenyl)-5-methyloxazol-4-yl]-ethyl bromide 140, followed by desilylation, and reaction with 1-(4-carbomethoxyphenyl)-1-(8-hydroxyoctyloxyphenyl)ethylene, 93 to afford the ether-linked dimer 103 and dicarboxylic acid 104.



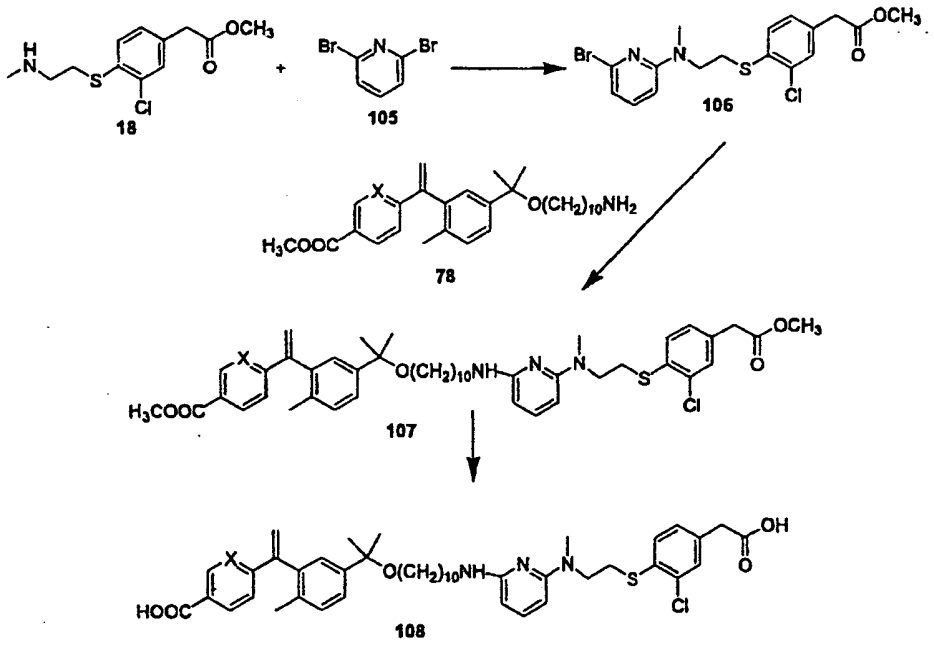
A. Using the alkylation conditions of Preparation 1C, (2S) methyl 2-(2-benzoylphenyl)amino-3-(4-hydroxyphenyl) propionate 7, prepared as described in J. Med. Chem., 1998, 41, 5020, is reacted with the compound 140 to afford the ether product. The ether product (1 mmol) is dissolved in THF (10 mL) and Bu_4NF (1 mmol) in THF is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford compound 102.

B. Using the Mitsonobu reaction conditions of Preparation 1A, the compound

102, is reacted with 93, to afford the dimer 103.

C. Using the hydrolysis procedure of Example 1B, the diester 103 is converted into the dicarboxylic acid 104.

Example 4: Reaction of methyl 4-(2-methylaminoethylthio)-3-chlorophenyl acetate 18 with 2,6-dibromopyridine 105 to afford the compound 106, and reaction of the product with 1-[3-(13-amino-2-methyl-3-oxa-2-tridecanyl)-6-methylphenyl)-1-(4-carbomethoxyphenyl)ethylene 78 to afford the compound 108 in which X is CH.



A. The amine 18 (1 mmol), diisopropylethylamine (1 mmol) and 2,6-dibromopyridine 105 (1 mmol) are dissolved in MeCN (25 mL). The mixture is heated at 60° and the progress of the reaction is monitored by tlc. When it is complete, the cooled mixture is added to water and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 106.

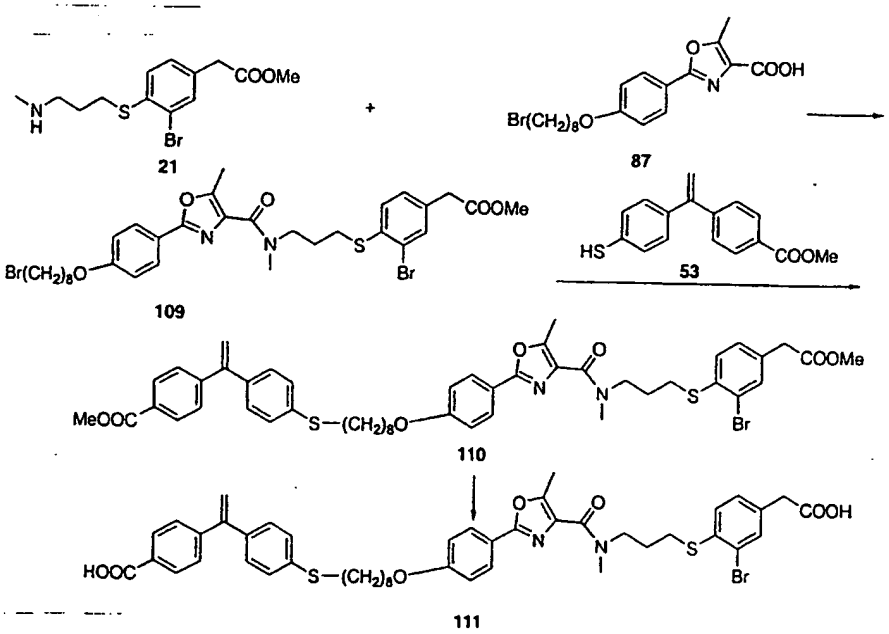
B. The compound 106 (1 mmol) and the amine 78, in which X is CH, (1

mmol) are dissolved in DMF (10 mL) containing K_2CO_3 (250 mg). The mixture is heated at 80° and the progress of the reaction is monitored by tlc. When it is complete, the cooled mixture is added to water and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 107, in which X is CH.

C. Using the hydrolysis procedure of Example 1B, the diester 107 is converted into the dicarboxylic acid 108 in which X is CH.

D. Using the above procedures, but employing in Step B, the compound 78, in which X is N, in place of the compound 78 in which X is CH, there is obtained the compound 108 in which X is N.

Example 5: Reaction between methyl 3-bromo-4-[(3-methylaminopropyl)mercapto]phenylacetate, 21 and 2-[4-(8-bromooctyloxy)phenyl]-5-methyloxazole-4-carboxylic acid 87 to afford the compound 109, and the reaction of 109 with 1-(4-carbomethoxyphenyl)-1-(4-mercaptophenyl)ethylene 53 to afford the compound 111.



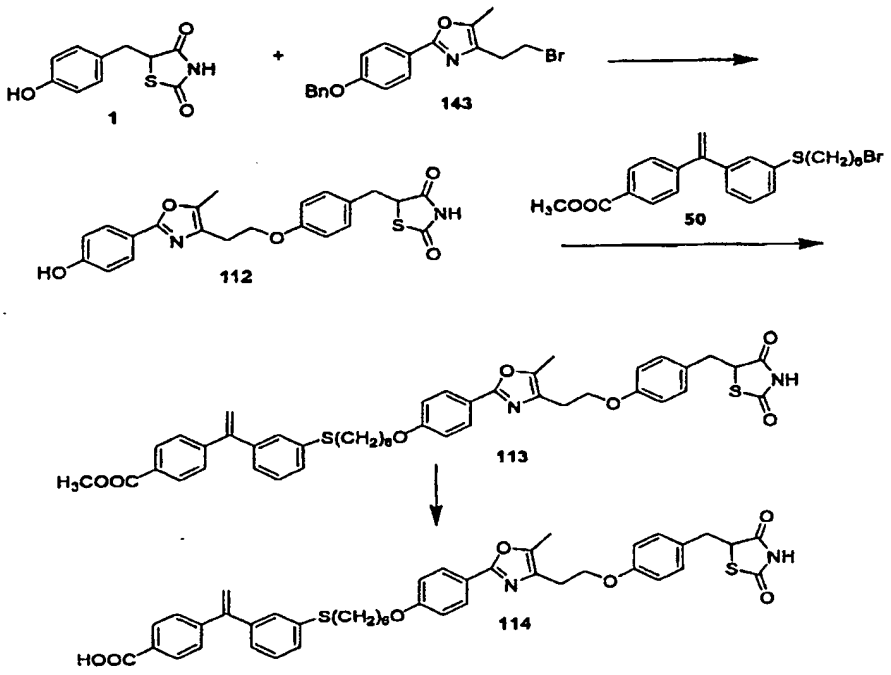
A. The amine 21 (1 mmol) and the carboxylic acid 87 (1 mmol) are dissolved

in DMF (20 mL) containing DCC (1 mmol). The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the amide 109.

B. The bromo compound 109 (1 mmol), diisopropylethylamine (1 mmol) and the mercaptan 53 (1 mmol) are dissolved in DMF (20 mL). The progress of the reaction is monitored by tlc. When it is complete, the cooled mixture is added to water and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 110.

C. Using the hydrolysis procedure of Example 1B, the diester 110 is converted into the dicarboxylic acid 111.

Example 6: Reaction between 5-[(4-Hydroxyphenyl)methyl]-2,4-thiazolidinedione, 1 and 2-[2-(4-benzyloxyphenyl)-5-methyloxazol-4-yl]-ethyl bromide 143, followed by debenzylation, to afford the compound 112, and reaction of 112 with 1-[3-(6-bromohexylthio)phenyl]-1-[4-carbomethoxyphenyl)ethylene, 50 to afford the dimer 113 and the carboxylic acid 114.

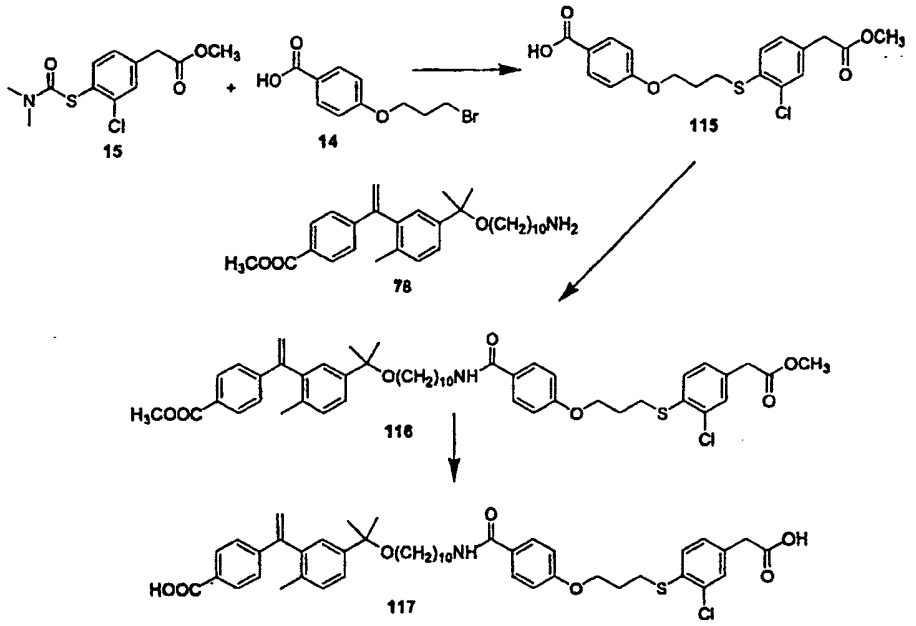


A. Using the alkylation conditions of Preparation 1C, 5-[(4-Hydroxyphenyl)methyl]-2,4-thiazolidinedione 1, prepared as described in Chem. Pharm, Bull., 1982, 30, 3580, is reacted with 2-[2-(4-benzyloxyphenyl)-5-methyloxazol-4-yl]-ethyl bromide, 143 to afford the ether product. The ether (1 mmol) is dissolved in EtOH (20 mL) and 10% Pd/C (0.01 g) is added. The mixture is hydrogenated in a Parr shaker at 10 psi. The progress of the reaction is monitored by tlc. When it is complete, the solution is filtered and the solvent is removed under vacuum. The residue is chromatograpbed to afford the deprotected compound 112.

B. Using the alkylation conditions of Preparation 1C, 1-[3-(6-bromohexylthio)phenyl]-1-[4-carbomethoxyphenyl]ethylene, 50 is reacted with compound 112 to afford the dimer 113.

C. Using the hydrolysis procedure of Example 1B, the ester 113 is converted into the carboxylic acid 114.

Example 7: Reaction between 3-chloro-4-dimethylaminocarbamoyl thiophenylacetic acid methyl ester 15 and 4-(3-bromopropyloxy)-benzoic acid 13 to afford 115, and reaction of compound 115 with 1-[3-(13-amino-2-methyl-3-oxa-2-tridecanyl)-6-methylphenyl)-1-(4-carbomethoxyphenyl)ethylene 78, in which X is CH, to afford the amide dimer 116 and the dicarboxylic acid 117.

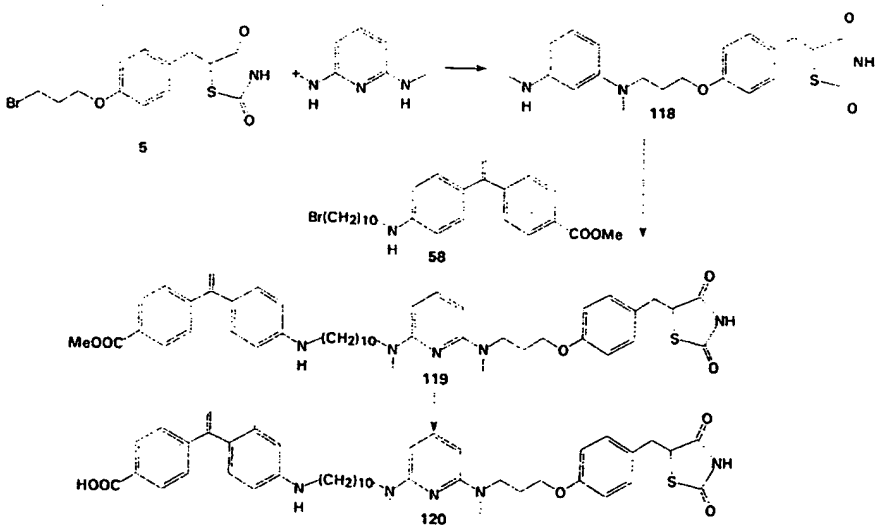


A. 3-chloro-4-dimethylaminocarbamoylthiophenylacetic acid methyl ester 15 (US Patent 5,859,051) (10 mmol) is dissolved in 25 mL of MeOH and added to a 0.5M solution (10 mmol, 20 mL) of sodium methoxide and heated to 70°C for 2 h. The reaction is cooled to room temperature, 10 mmol of 4-(3-bromopropyloxy)-benzoic acid 13 (J. Amer. Chem. Soc. 1951, 73, 3159-3160) is added, and the reaction is heated to 60°C for 12 h. The reaction is cooled, concentrated in vacuo to approximately 2 mL, diluted with ethyl acetate, neutralized with 1N HCl, and the organic layer is separated, washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product is chromatographed to afford compound 115.

B. The amine 78 (1 mmol) and the carboxylic acid 115 (1 mmol) are dissolved in DMF (20 mL) and DCC (1 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the amide dimer 116.

C. Using the hydrolysis procedure of Example 1B, the diester 116 is converted into the dicarboxylic acid 117.

Example 8: Reaction between 5-[4-(3-bromopropyloxy)phenyl]methyl-2,4-thiazolidinedione, 5 and 2,6-di(methylamino)pyridine, to afford the compound 118, and reaction of 118 with 1-[4-(10-bromodecylamino)phenyl]-1-(4-carbomethoxyphenyl)-ethylene, 58 to afford the compound 120.

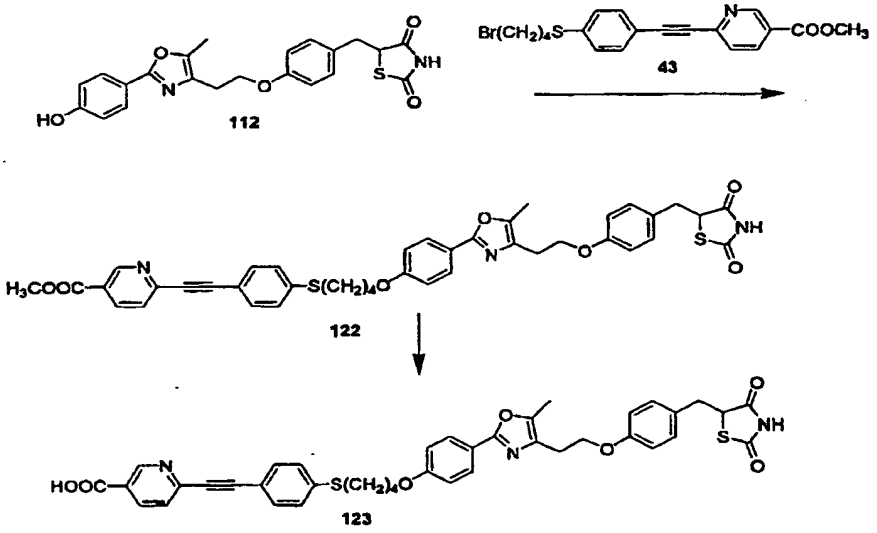


A. The bromo compound 5 (1 mmol) and 2,6-di(methylamino)pyridine (1 mmol) are dissolved in DMF (20 mL) containing K_2CO_3 (250 mg). The mixture is heated to 70°, and the progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 118.

B. The amine 118 (1 mmol) and the bromo compound 58 (1 mmol) are dissolved in DMF (20 mL) containing K_2CO_3 (250 mg). The mixture is heated at 70°. The progress of the reaction is monitored by tlc. When the reaction is complete, the mixture is added to water and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 119.

C. Using the hydrolysis procedure of Example 1B, the ester 119 is converted into the carboxylic acid 120.

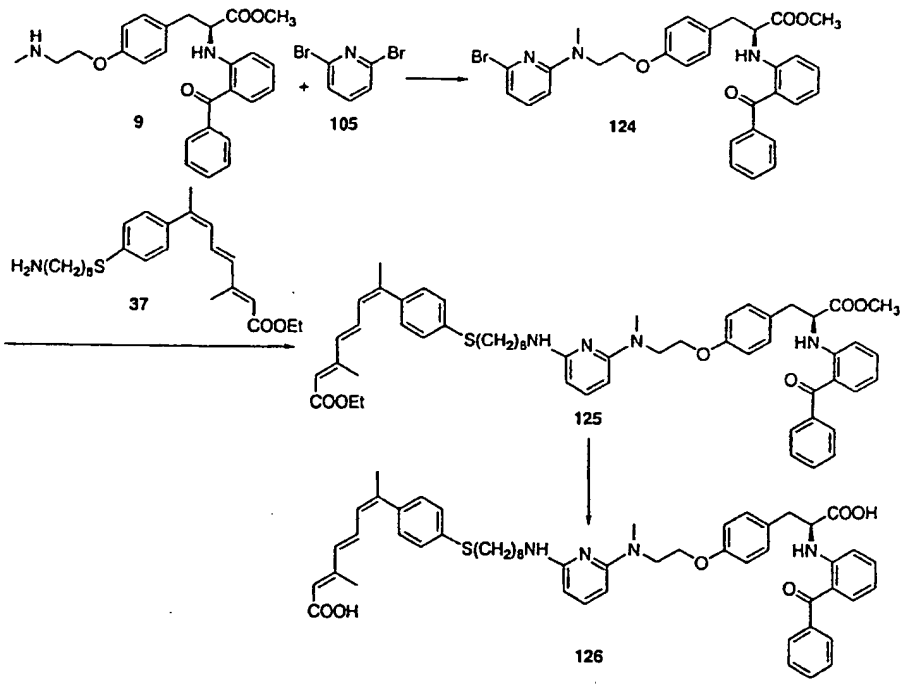
Example 9: Reaction of compound 112 with methyl 2-[4-(4-bromobutylthio)phenylethynyl]pyridine-5-carboxylate, 43 to afford the dimer compound 122 and the dicarboxylic acid 123.



A. The phenol compound 112 (1 mmol) is dissolved in DMF (20 mL) and 50 % NaH in oil (1 mmol) is added. When hydrogen evolution has ceased, the bromo compound 43 (1 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 122.

B. Using the hydrolysis procedure of Example 1B, the ester dimer 122 is converted into the dicarboxylic acid 123.

Example 10: Reaction between (2S) methyl 2-(2-benzoylphenyl)amino-3-[4-(2-methylamino)ethoxyphenyl] propionate, 9 and 2,6-dibromopyridine 105, to afford the compound 124, and reaction of 124 with ethyl 3,7-dimethyl-7-[4-(8-aminooctylthio)phenyl]hepta-2(E),4(E),6(E)-trienoate, 37 to afford the compound 126.



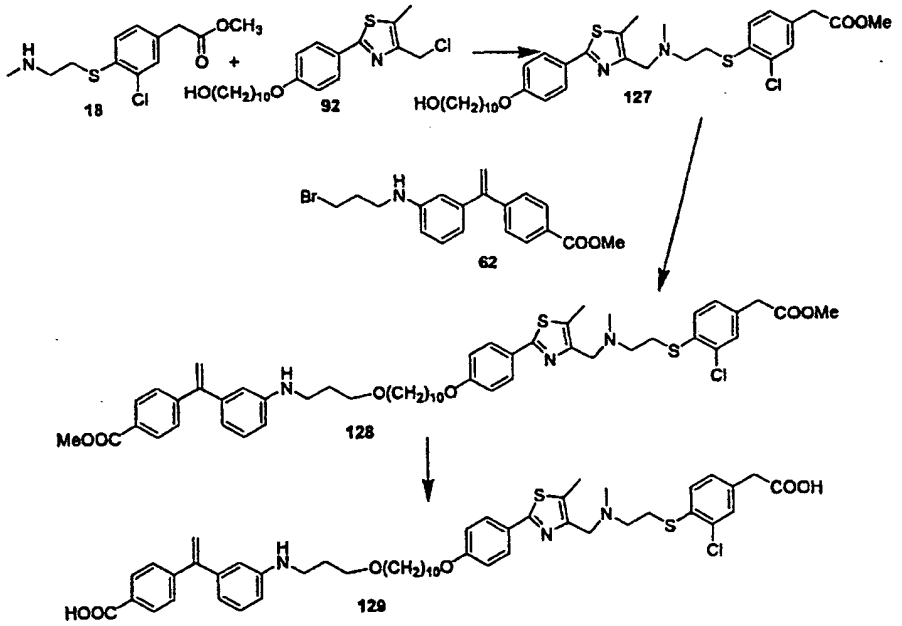
A. The amine 9 (1 mmol), 2,6-dibromopyridine 105 (1 mmol) and diisopropylethylamine (1 mmol) are dissolved in DMF (20 mL). The mixture is heated at 70°. The progress of the reaction is monitored by tlc. When it is complete, the cooled mixture is added to water and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 124.

B. The bromo compound 124 (1 mmol) and the amine 37 (1 mmol) are

dissolved in DMF (20 mL) containing K_2C0_3 (250 mg). The mixture is heated at 70°. The progress of the reaction is monitored by tlc. When it is complete, the cooled mixture is added to water and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 125.

C. Using the hydrolysis procedure of Example 1, the diester 125 is converted into the dicarboxylic acid 126.

Example 11: Reaction between methyl 4-(2-methylaminoethylthio)-3-chlorophenyl acetate, 18 and 4-chloromethyl-2-[4-(10-hydroxydecyloxy)phenyl]-5-methylthiazole, 92 to afford the compound 127, and reaction of 127 with 1-[3-(3-bromopropylamino)phenyl]-1-(4-carbomethoxyphenyl)-ethylene, 62 to afford the compound 128 and the dicarboxylic acid 129.



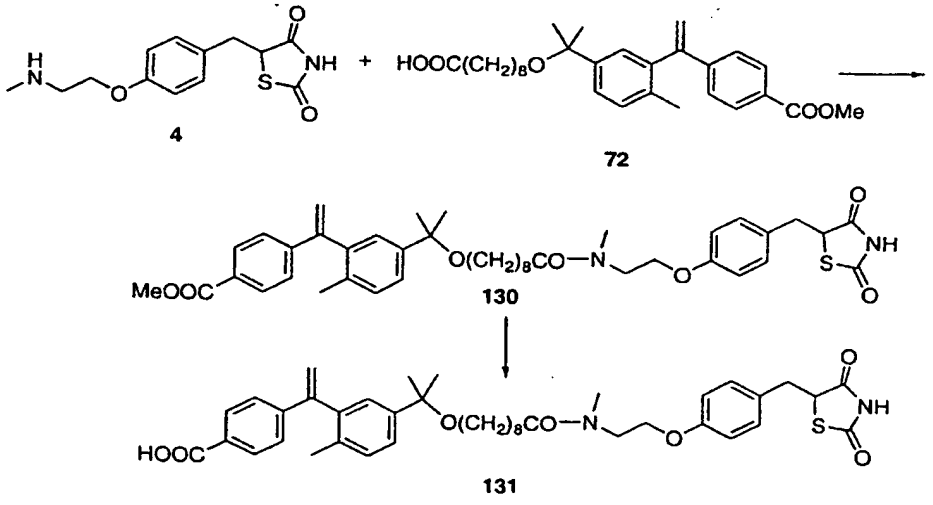
A. The chloromethyl compound 92 (1 mmol) and the amine 18 (1 mmol) are dissolved in MeCN (20 mL) containing diisopropylethylamine (1 mmol).

The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 127.

B. The compound 127 (1 mmol) is dissolved in DMF (20 mL) and 50% NaH in oil (1 mmol) is added. When hydrogen evolution has ceased, the bromo compound 62 (1 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 128.

C. Using the hydrolysis procedure of Example 1B, the diester 128 is converted into the dicarboxylic acid 129.

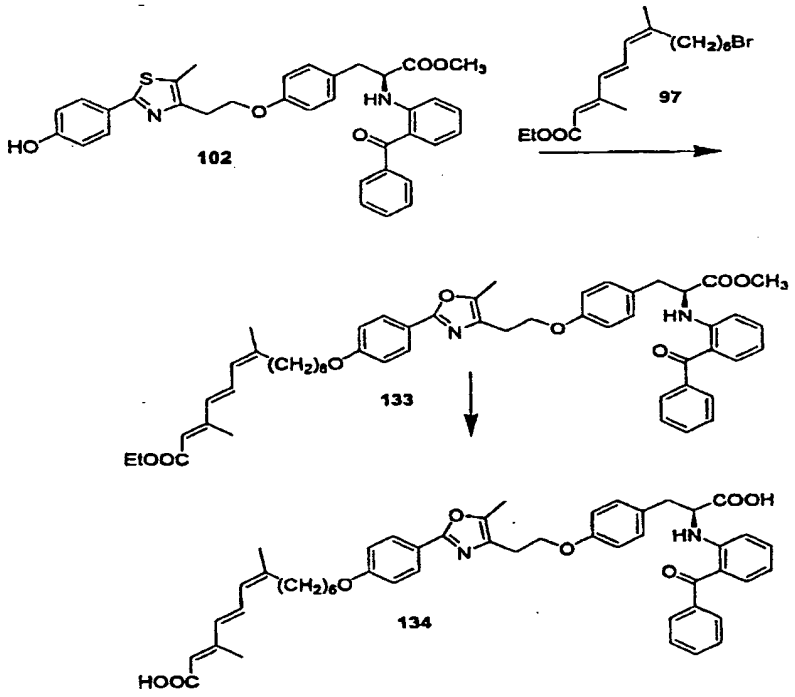
Example 12: Reaction between 5-[4-(2-methylaminoethoxy)phenyl]methyl-2,4-thiazolidinedione, 4 and 1-[3-(11-carboxy-2-methyl-3-oxa-2-undecyl)phenyl]-1-(4-carbomethoxyphenyl)ethylene, 72 to afford the compound 131.



A. The amine 4 (1 mmol), the carboxylic acid 72 (1 mmol) and DCC (1 mmol) are dissolved in DMF (20 mL). The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 130.

B. Using the hydrolysis procedure of Example 1B, the ester 130 is converted into the carboxylic acid 131.

Example 13: Reaction between compound 102 and ethyl 13-bromo-3,7-dimethyltrideca-2(E),4(E),6(E)-trienoate, 97 to afford the ether-linked compound 133 and dicarboxylic acid 134.

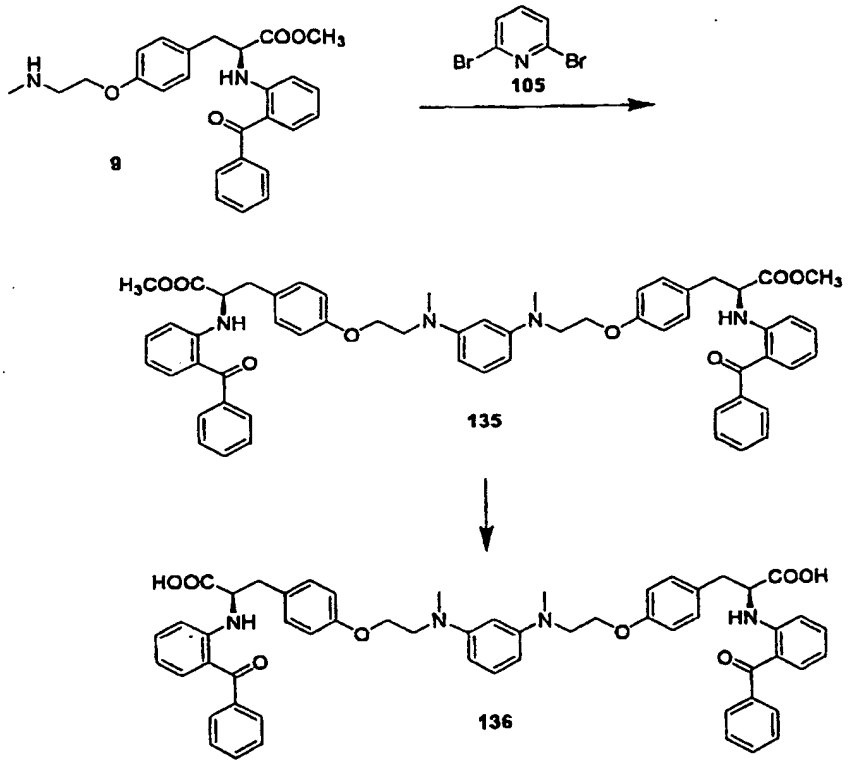


A. Using the alkylation conditions of Preparation 1C, compound 102 is reacted with ethyl 13-bromo-3,7-dimethyltrideca-2(E),4(E),6(E)-trienoate, 97 to afford the ether dimer product 133.

B. Using the hydrolysis procedure of Example 1B, the diester 133 is converted

into the dicarboxylic acid 134.

Example 14: Reaction between (2S) methyl 2-(2-benzoylphenyl)amino-3-[4-(2-methylamino)ethoxyphenyl] propionate, 9 with 2,6-dibromopyridine 105 to afford the dimer compound 135, and the carboxylic acid 136.



A. The amine 9 (1 mmol) diisopropylediylamine (1 mmol) and 2,6-dibromopyridine 105 (0.5 mmol) are dissolved in MeCN (15 mL). The mixture is heated at 100° and the progress of the reaction is monitored by tlc. When it is complete, the cooled mixture is added to water and extracted with CH_2Cl_2. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 135.

B. Using the hydrolysis procedure of Example 1B, the diester 135 is converted into the dicarboxylic acid 136.

The foregoing examples are illustrative only. One of skill in the art will recognize that variations of reactants and conditions will result in different end products still within the scope of the invention.

WHAT IS CLAIMED IS:

1. A multibinding compound represented by Formula I:

$$(L)_p(X)_q \qquad (I)$$

and pharmaceutically acceptable salts thereof;

wherein:

each L is a ligand that may be the same or different at each occurrence;

each X is a linker that may be the same or different at each occurrence;

p is an integer of from 2 to 10; and

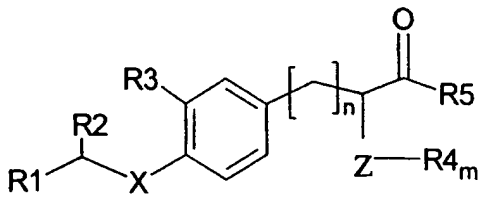
q is an integer of from 1 to 20;

wherein each of said ligands comprises a ligand domain capable of binding to one of a RXR receptor or a PPARγ receptor, and where *q* is less than *p*,

with the proviso that when one L is a ligand domain capable of binding to a RXR receptor, at least one other L must be a ligand domain capable of binding to a PPARγ receptor.

2. The multibinding compound of claim 1, wherein each of said ligands is capable of increasing the effects of insulin while decreasing plasma glucose, insulin and triglyceride levels in an insulin-resistant mammal.

3. The multibinding compound of claim 2, wherein the ligand capable of binding to a PPARγ receptor independently comprises a group of Formula A:



(A)

wherein

R1 is selected from OH, alkyl, substituted alkyl, alkoxy, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, aryloxy, heteroaryl, and substituted heteroaryl;

R2 is selected from hydrogen or alkyl;

R3 is selected from hydrogen, alkyl, substituted alkyl, I, Br, Cl or F;

R4 is selected from alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R5 is H, OH, NH_2, or alkoxy, or R4 and R5 together form -C(O)-NH-;

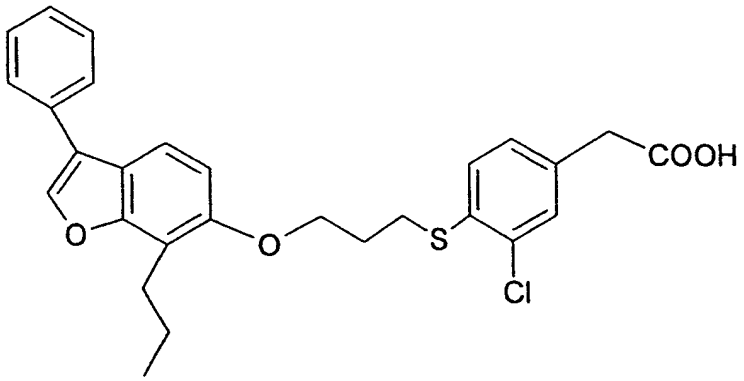
X is -O-, $-CH_2-$, -CH-, -S-, or -NH-; where X is O, R2 and R3 together form $-CH_2-CH_2-$; where X is -CH-, R2 and R3 together form =CH-CH= creating a benzene ring; and

Z is S, NH, H, $-CH_2$ -, alkyl, or substituted alkyl; where Z is H, alkyl or substituted alkyl, m=0; else m is 1;

n is 0 or 1,

or derivatives thereof.

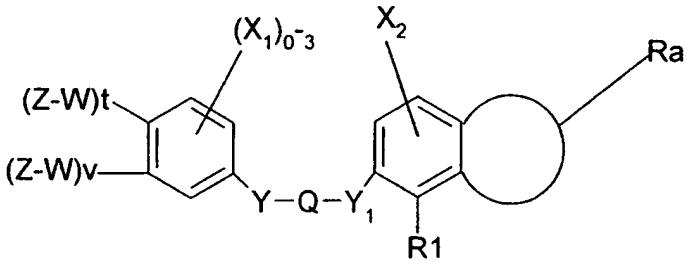
4. The multibinding compound of claim 2, wherein the ligand capable of binding to a PPARγ receptor independently comprises a group of Formula B:



(B)

and derivatives thereof.

5. The multibinding compound of claim 2, wherein the ligand capable of binding to a PPARγ receptor independently comprises a group of Formula C:



(C)

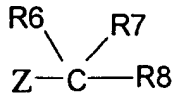
wherein:

R is selected from the group consisting of H, C1-6 alkyl, C5-10 aryl, and C5-10 heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of Ra;

R1 is selected from a group consisting of: H, C1-15 alkyl, C2-15 alkenyl, C2-15 alkynyl and C3-10 cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of Ra;

R3 is selected from a group consisting of: H, NHR1, NHacyl, C1-15 alkyl, C3-10 cycloalkyl, C2-15 alkenyl, C1-15 alkoxy, CO_2 alkyl, OH, C2-15 alkynyl, C5-10 aryl, C5-10 heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of Ra;

(Z--W--) is Z--CR6R7 --, Z--CH=CH--, or



R8 is selected from the group consisting of CR6R7, O, NR6, and $S(O)_p$;

R6 and R7 are independently selected from the group consisting of H, C1-6 alkyl;

B is selected from the group consisting of:

1) a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 1 heteroatom selected from the group consisting of O, S and N, heteroatom

being substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of Ra;

2) a 5 or 6 membered carbocycle containing 0 to 2 double bonds, the carbocycle optionally unsubstituted or substituted with 1 to 3 groups of Ra at any position on the five or six membered carbocycle; and

3) a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 3 heteroatoms selected from the group consisting of O, N, and S, which are substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of Ra;

X1 and X2 are independently selected from a group consisting of: H, OH, C1-15 alkyl, C2-15 alkenyl, C2-15 alkynyl, halo, OR3, $ORCF_3$, C5-10 aryl, C5-10 aralkyl, C5-10 heteroaryl and C1-10 acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of Ra;

Ra represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, --O--, CN, NO_2, R3, OR3, SR3, =N(OR), S(O)R3, SO_2R3, NR3, R3, NR3 COR3, NR3 CO_2R3, NR3CON$(R3)_2$, NR3SO_2R3, COR3, CO_2R3, CON$(R3)_2$, SO_2N$(R3)_2$, OCON$(R3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

Y is selected from the group consisting of: S(O)*p*, --CH_2 --, --C(O)--, --C(O)NH--, --NR--, --O--, --SO_2NH, --$NHSO_2$;

Y1 is selected from the group consisting of: O and C;

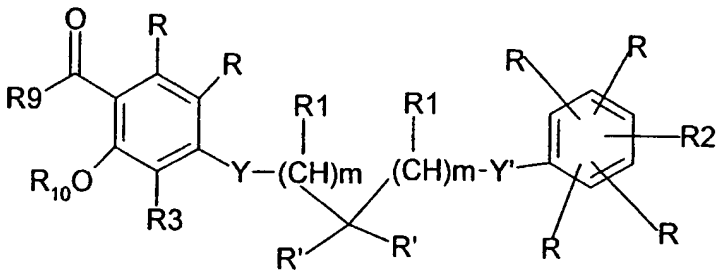
Z is selected from the group consisting of: CO_2R3, R3CO_2R3, CONHSO_2Me, $CONH_2$ and 5-(1H-tetrazole);

t and v are independently 0 or 1 such that t+v=1;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and p is 0-2 with the proviso when Z is CO_2R3 and B is a 5 membered heterocycle consisting of O, R3 does not represent methyl;

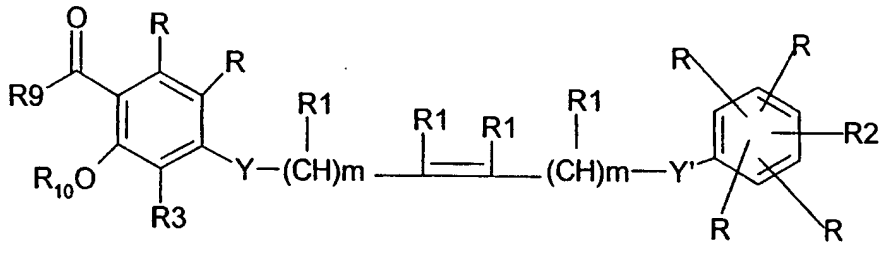
and derivatives thereof.

6. The multibinding compound of claim 2, wherein the ligand capable of binding to a PPARγ receptor independently comprises a group selected from Formula D:



(D)

or Formula E:

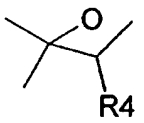


(E)

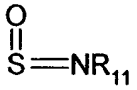
wherein:

each R is independently H, OH, alkyl of 1 to 6 carbon atoms which may be straight chain or branched; alkenyl of 2 to 6 carbon atoms which may be straight chain or branched; trifluoromethyl; alkoxy of 1 to 6 carbon atoms which may be straight chain or branched; SH; thioalkyl of 1 to 6 carbon atoms which may be straight chain or branched; phenyl; phenyl substituted by alkyl of 1 to 3 carbon atoms or by halogen; benzyl; phenethyl; halogen, amino; $N(R4)_2$ wherein R4 is H or alkyl of 1 to 6 carbon atoms which may be straight chain or branched; COOR4; CH_2OR4 ; formyl; CN; trifluoromethylthio; or nitro;

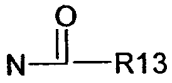
each R' is independently R4 ; OR4 ; COOR4 ; $N(R4)_2$; SR4 ; CH_2OR4 ; CHO; or together R' and R' are O; CH2 ; or



Y' is sulfur, sulfoxide, sulfone;



R11 is H, alkyl of 1-4 carbon atoms which may be straight chain or branched; alkanoyl of 1-4 carbon atoms which may be straight chain or branched; phenylsulfonyl; tosyl; NR12 wherein R12 is H, alkyl of 1-4 carbon atoms which may be straight chain or branched; or



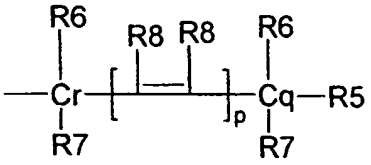
wherein R13 is alkyl of 1-4 carbon atoms which may be straight chain or branched, alkoxy of 1-4 carbon atoms which may be straight chain or branched; N--CN, CH_2, or C=O;

Y is Y' and oxygen;

each R1 is independently hydrogen or alkyl of 1-3 carbon atoms;

each m is independently an integer from 0-6;

R2 is

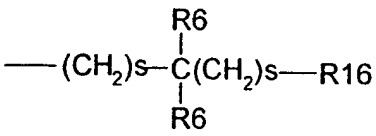


each R6 is independently H or alkyl of 1-4 carbons;

each R7 is independently H, OH, or alkyl of 1-4 carbons;

each R8 is independently H, or alkyl of 1-4 carbons, and is absent when a triple bond is present;

R5 is COOR4 ; CH_2OH; CHO; tetrazole; $NHSO_2R14$; hydroxymethylketone; CN; $CON(R7)_2$; a monocyclic or bicyclic heterocyclic ring containing an acidic hydroxyl group; or COOR15 where R15 is



wherein each s is independently 0-3;

R16 is A) a monocyclic or bicyclic heterocyclic radical containing from 3 to 12 nuclear carbon atoms and 1 or 2 nuclear heteroatoms selected from N and S with at least one being N, and with each ring in the heterocyclic radical being formed of 5 or 6 atoms, or

B) the radical W--R17 wherein W is O, S or NH and R17 contains up to 21 carbon atoms and is (1) a hydrocarbon radical or (2) an acyl radical of an organic acyclic or monocyclic carboxylic acid containing not more than 1 heteroatom in the ring;

R14 is OH, alkyl or alkoxy of 1 to 6 carbon atoms, phenyl or phenyl substituted by alkyl or alkoxy groups of 1 to 3 carbon atoms, halogen, hydroxy, haloalkyl, COOH, CN, formyl, acyl of 1 to 6 carbon atoms or perfluoroalkyl of 1 to 4 carbon atoms;

r and q are each independently 0-20 provided that the total of r and q does not exceed 20;

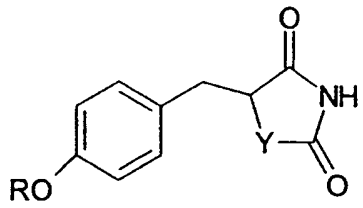
p is 0 or 1;

R9 is alkyl of 1 to 6 carbon atoms which may be straight chain or branched; alkoxy of 1 to 6 carbon atoms which may be straight chain or branched; or $(CH_2)_rR5$; and

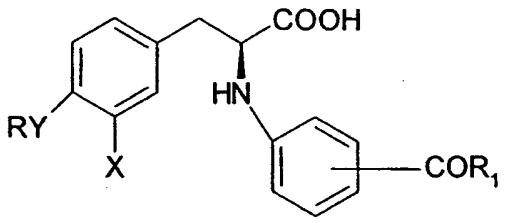
R10 is H; alkyl of 1 to 6 carbon atoms which may be straight chain or branched; R4C(O) or R4OCH$_2$,

or derivatives thereof.

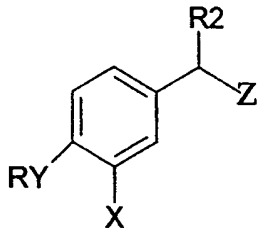
7. The multibinding compound of claim 2, wherein the ligand capable of binding to a PPARγ receptor independently comprises a group selected from one of the Formulas F-K:



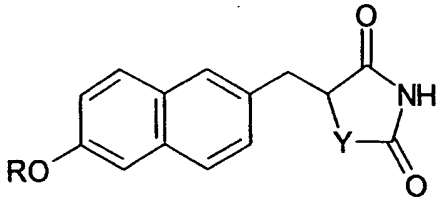
F



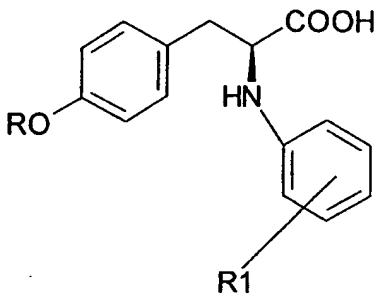
G



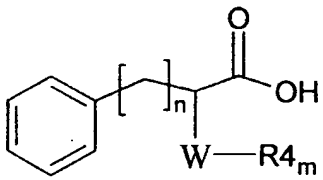
H



I



J



K

wherein

R is selected from alkyl, substituted alkyl, alkaryl, acyl, acylamino, cycloalkyl, hetocyclic, aryl, substituted aryl, and heteroaryl;

R1 is selected from alkyl, substituted alkyl, alkaryl, acyl, acylamino, cycloalkyl, heterocyclic, aryl, substituted aryl, and heteroaryl, and preferably R1 is an the ortho position;

R2 is selected from alkyl, substituted alkyl and hydrogen;

R4 is selected from alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

m is 0 when W is H, alkyl or substituted alkyl; else m is 1.

W is selected from S, NH, H, -CH2-, alkyl, or substituted alkyl

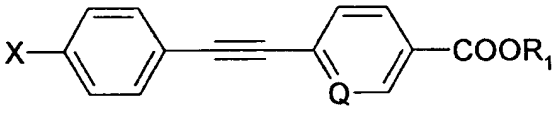
X is selected from I, F, Cl, Br, H, alkyl, and substituted alkyl;

Y is selected from S, O and N;

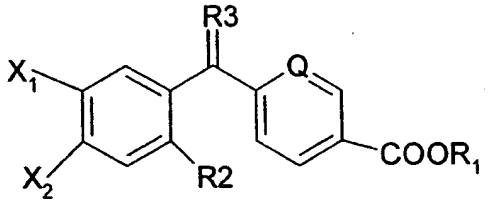
Z is selected from the group consisting of: C(O)H, CO_2R3, $R3CO_2R3$, $CONHSO_2Me$, $CONH_2$ and 5-(1H-tetrazole); wherein R3 is selected from a group

consisting of: H, NHR1, NHacyl, C1-15 alkyl, C3-10 cycloalkyl, C2-15 alkenyl, C1-15 alkoxy, CO_2 alkyl, OH, C2-15 alkynyl, C5-10 aryl, C5-10 heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of Ra; and wherein Ra represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, --O--, CN, NO_2, R3, OR3 ; SR3, =N(OR), S(O)R3, SO_2R3, NR3, R3, NR3COR3, $NR3CO_2R3$, $NR3CON(R3)_2$, $NR3SO_2R3$, COR3, CO_2R3, $CON(R3)_2$, $SO_2N(R3)_2$, $OCON(R3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl.

8. The multibinding compound of claim 2, wherein the ligand capable of binding to a RXR receptor independently comprises a group selected from one of the Formulas II-IV:



(II)



(III)

$$XR—(A)n—COOR_1 \qquad (IV)$$

wherein

X, X1 and X2 are independently selected from the group consisting of H, OH, I, Br, Cl, F, Na, SH, O, NH, carbonyl, amide, alkyl, alkoxy, aryl, aryloxy, and alkaryl;

R is aryl, substituted aryl, alkyl, substituted alkyl, heteroaryl, or substituted heteroaryl;

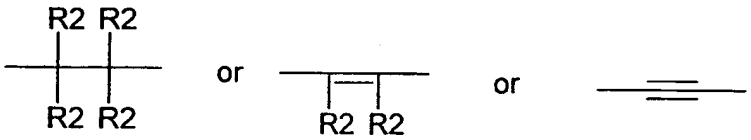
R1 is H or alkyl;

R2 is H or alkyl;

R3 is CH_2, O, or NOR4 wherein R4 is alkyl or substituted alkyl;

Q is CH or N,

A is



and n is 1-10,

or derivatives thereof.

9. The multibinding compound of claim 2, wherein each divalent linker X is independently selected from a structure of Table 1.

10. The multibinding compound of claim 9, wherein *p* is an integer of from 2 to 4, and *q* is less than *p*.

11. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of one or more multibinding compounds represented by Formula I,

$$(L)_p(X)_q \qquad (I)$$

and pharmaceutically acceptable salts thereof;

wherein:

each L is a ligand that may be the same or different at each occurrence;

each X is a linker that may be the same or different at each occurrence;

p is an integer of from 2 to 10; and

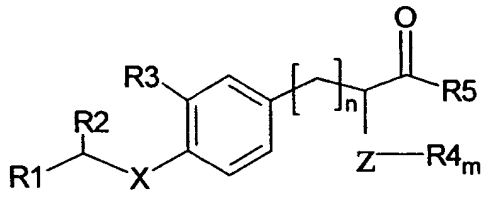
q is an integer of from 1 to 20;

wherein each of said ligands comprises a ligand domain capable of binding to one of a RXR receptor or a PPARγ receptor, and where q is less than p,

with the proviso that when one L is a ligand domain capable of binding to a RXR receptor, at least one other L must be a ligand domain capable of binding to a PPARγ receptor.

12. The pharmaceutical composition of claim 11, wherein said multibinding compound or compounds is capable of increasing the effects of insulin while decreasing plasma glucose, insulin and triglyceride levels in an insulin-resistant mammal.

13. The pharmaceutical composition of claim 12, wherein each of said ligands independently comprises a group selected from one of Formulas A - K:



(A)

wherein

R1 is selected from OH, alkyl, substituted alkyl, alkoxy, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, aryloxy, heteroaryl, and substituted heteroaryl;

R2 is selected from hydrogen or alkyl;

R3 is selected from hydrogen, alkyl, substituted alkyl, I, Br, Cl or F;

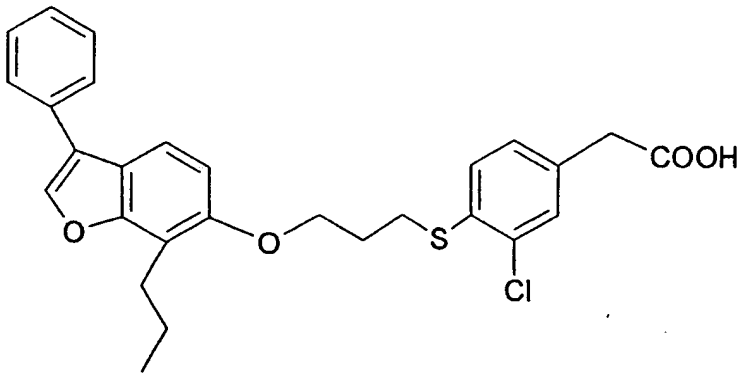
R4 is selected from alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R5 is H, OH, NH_2, or alkoxy, or R4 and R5 together form -C(O)-NH-;

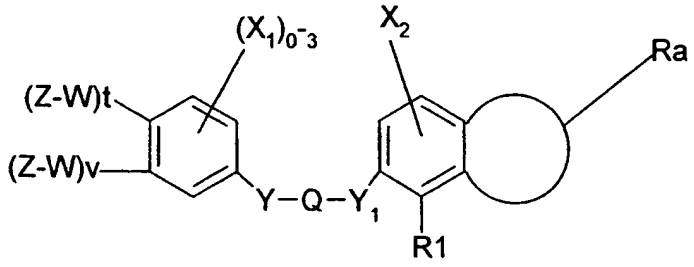
X is -O-, $-CH_2-$, -CH-, -S-, or -NH-; where X is O, R2 and R3 together form $-CH_2-CH_2-$; where X is -CH-, R2 and R3 together form =CH-CH= creating a benzene ring; and

Z is S, NH, H, $-CH_2$ -, alkyl, or substituted alkyl; where Z is H, alkyl or substituted alkyl, m=0; else m is 1;

n is 0 or 1;



(B)



(C)

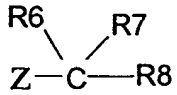
wherein:

R is selected from the group consisting of H, C1-6 alkyl, C5-10 aryl, and C5-10 heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of Ra;

R1 is selected from a group consisting of: H, C1-15 alkyl, C2-15 alkenyl, C2-15 alkynyl and C3-10 cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of Ra;

R3 is selected from a group consisting of: H, NHR1, NHacyl, C1-15 alkyl, C3-10 cycloalkyl, C2-15 alkenyl, C1-15 alkoxy, CO_2 alkyl, OH, C2-15 alkynyl, C5-10 aryl, C5-10 heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of Ra;

(Z--W--) is Z--CR6R7 --, Z--CH=CH--, or



R8 is selected from the group consisting of CR6R7, O, NR6, and $S(O)_p$;

R6 and R7 are independently selected from the group consisting of H, C1-6 alkyl;

B is selected from the group consisting of:

1) a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 1 heteroatom selected from the group consisting of O, S and N, heteroatom being substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of Ra;

2) a 5 or 6 membered carbocycle containing 0 to 2 double bonds, the carbocycle optionally unsubstituted or substituted with 1 to 3 groups of Ra at any position on the five or six membered carbocycle; and

3) a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 3 heteroatoms selected from the group consisting of O, N, and S, which are substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of Ra;

X1 and X2 are independently selected from a group consisting of: H, OH, C1-15 alkyl, C2-15 alkenyl, C2-15 alkynyl, halo, OR3, $ORCF_3$, C5-10 aryl,

C5-10 aralkyl, C5-10 heteroaryl and C1-10 acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of Ra;

Ra represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, --O--, CN, NO_2, R3, OR3, SR3, =N(OR), S(O)R3, SO_2R3, NR3, R3, NR3 COR3, NR3 CO_2R3, NR3CON$(R3)_2$, NR3SO_2R3, COR3, CO_2R3, CON$(R3)_2$, $SO_2N(R3)_2$, OCON$(R3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

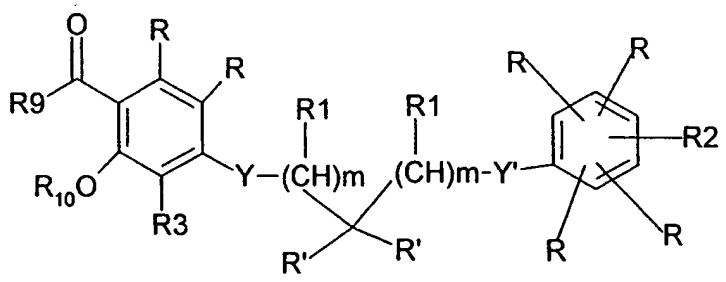
Y is selected from the group consisting of: S(O)*p*, --CH_2 --, --C(O)--, --C(O)NH--, --NR--, --O--, --SO_2NH, --$NHSO_2$;

Y1 is selected from the group consisting of: O and C;

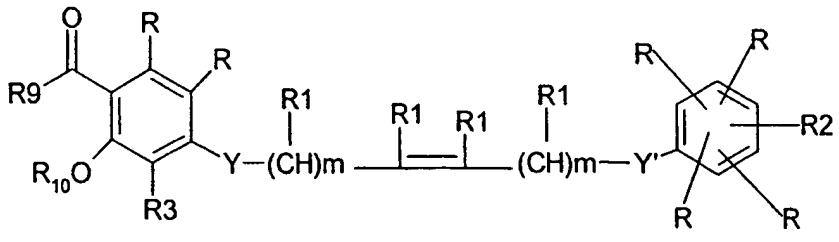
Z is selected from the group consisting of: CO_2R3, $R3CO_2R3$, $CONHSO_2Me$, $CONH_2$ and 5-(1H-tetrazole);

t and v are independently 0 or 1 such that t+v=1;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and p is 0-2 with the proviso when Z is CO_2R3 and B is a 5 membered heterocycle consisting of O, R3 does not represent methyl;



(D)

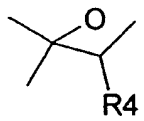


(E)

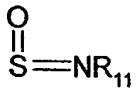
wherein:

each R is independently H, OH, alkyl of 1 to 6 carbon atoms which may be straight chain or branched; alkenyl of 2 to 6 carbon atoms which may be straight chain or branched; trifluoromethyl; alkoxy of 1 to 6 carbon atoms which may be straight chain or branched; SH; thioalkyl of 1 to 6 carbon atoms which may be straight chain or branched; phenyl; phenyl substituted by alkyl of 1 to 3 carbon atoms or by halogen; benzyl; phenethyl; halogen, amino; $N(R4)_2$ wherein R4 is H or alkyl of 1 to 6 carbon atoms which may be straight chain or branched; COOR4; CH_2OR4 ; formyl; CN; trifluoromethylthio; or nitro;

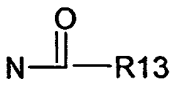
each R' is independently R4 ; OR4 ; COOR4 ; $N(R4)_2$; SR4 ; CH_2OR4 ; CHO; or together R' and R' are O; CH2 ; or



Y' is sulfur, sulfoxide, sulfone;



R11 is H, alkyl of 1-4 carbon atoms which may be straight chain or branched; alkanoyl of 1-4 carbon atoms which may be straight chain or branched; phenylsulfonyl; tosyl; NR12 wherein R12 is H, alkyl of 1-4 carbon atoms which may be straight chain or branched; or



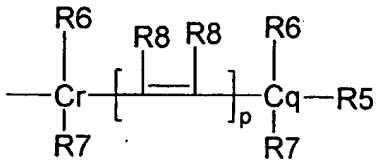
wherein R13 is alkyl of 1-4 carbon atoms which may be straight chain or branched, alkoxy of 1-4 carbon atoms which may be straight chain or branched; N--CN, CH_2, or C=O;

Y is Y' and oxygen;

each R1 is independently hydrogen or alkyl of 1-3 carbon atoms;

each m is independently an integer from 0-6;

R2 is

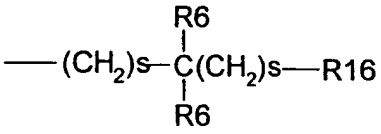


each R6 is independently H or alkyl of 1-4 carbons;

each R7 is independently H, OH, or alkyl of 1-4 carbons;

each R8 is independently H, or alkyl of 1-4 carbons, and is absent when a triple bond is present;

R5 is COOR4 ; CH_2OH; CHO; tetrazole; $NHSO_2R14$; hydroxymethylketone; CN; $CON(R7)_2$; a monocyclic or bicyclic heterocyclic ring containing an acidic hydroxyl group; or COOR15 where R15 is



wherein each s is independently 0-3;

R16 is A) a monocyclic or bicyclic heterocyclic radical containing from 3 to 12 nuclear carbon atoms and 1 or 2 nuclear heteroatoms selected from N and S with at least one being N, and with each ring in the heterocyclic radical being formed of 5 or 6 atoms, or

B) the radical W--R17 wherein W is O, S or NH and R17 contains up to 21 carbon atoms and is (1) a hydrocarbon radical or (2) an acyl radical of an organic acyclic or monocyclic carboxylic acid containing not more than 1 heteroatom in the ring;

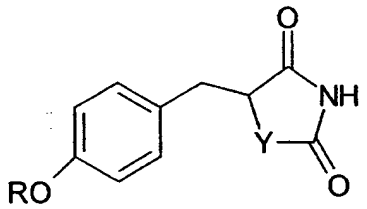
R14 is OH, alkyl or alkoxy of 1 to 6 carbon atoms, phenyl or phenyl substituted by alkyl or alkoxy groups of 1 to 3 carbon atoms, halogen, hydroxy, haloalkyl, COOH, CN, formyl, acyl of 1 to 6 carbon atoms or perfluoroalkyl of 1 to 4 carbon atoms;

r and q are each independently 0-20 provided that the total of r and q does not exceed 20;

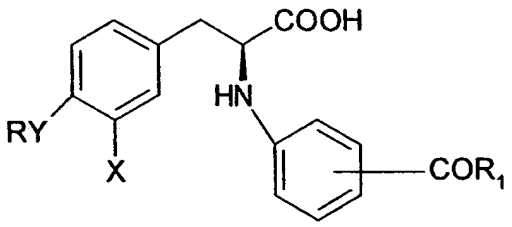
p is 0 or 1;

R9 is alkyl of 1 to 6 carbon atoms which may be straight chain or branched; alkoxy of 1 to 6 carbon atoms which may be straight chain or branched; or $(CH_2)_rR5$; and

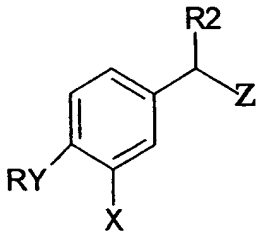
R10 is H; alkyl of 1 to 6 carbon atoms which may be straight chain or branched; R4C(O) or $R4OCH_2$;



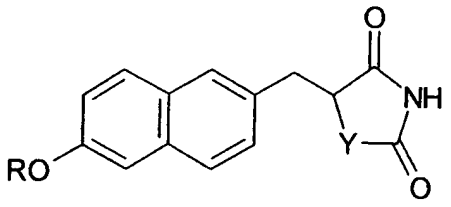
F



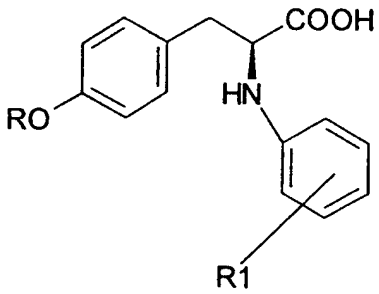
G



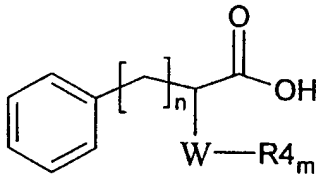
H



I



J



K

wherein

R is selected from alkyl, substituted alkyl, alkaryl, acyl, acylamino, cycloalkyl, hetocyclic, aryl, substituted aryl, and heteroaryl;

R1 is selected from alkyl, substituted alkyl, alkaryl, acyl, acylamino, cycloalkyl, heterocyclic, aryl, substituted aryl, and heteroaryl, and preferably R1 is an the ortho position;

R2 is selected from alkyl, substituted alkyl and hydrogen;

R4 is selected from alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

m is 0 when W is H, alkyl or substituted alkyl; else m is 1.

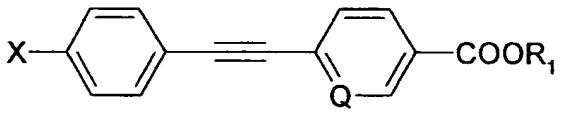
W is selected from S, NH, H, -CH2-, alkyl, or substituted alkyl

X is selected from I, F, Cl, Br, H, alkyl, and substituted alkyl;

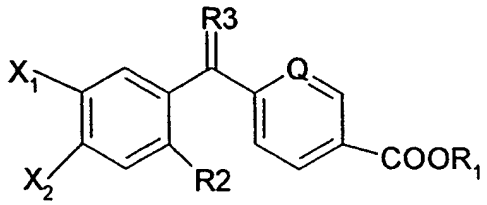
Y is selected from S, O and N;

Z is selected from the group consisting of: C(O)H, CO_2R3, $R3CO_2R3$, $CONHSO_2Me$, $CONH_2$ and 5-(1H-tetrazole); wherein R3 is selected from a group consisting of: H, NHR1, NHacyl, C1-15 alkyl, C3-10 cycloalkyl, C2-15 alkenyl, C1-15 alkoxy, CO_2 alkyl, OH, C2-15 alkynyl, C5-10 aryl, C5-10 heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of Ra; and wherein Ra represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, --O--, CN, NO_2, R3, OR3; SR3, =N(OR), S(O)R3, SO_2R3, NR3, R3, NR3COR3, $NR3CO_2R3$, $NR3CON(R3)_2$, $NR3SO_2R3$, COR3, CO_2R3, $CON(R3)_2$, $SO_2N(R3)_2$, $OCON(R3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

or selected from one of Formulas II-IV:



(II)



(III)

$XR—(A)n—COOR_1$ (IV)

wherein

X, X1 and X2 are independently selected from the group consisting of H, OH, I, Br, Cl, F, Na, SH, O, NH, carbonyl, amide, alkyl, alkoxy, aryl, aryloxy, and alkaryl;

R is aryl, substituted aryl, alkyl, substituted alkyl, heteroaryl, or substituted heteroaryl;

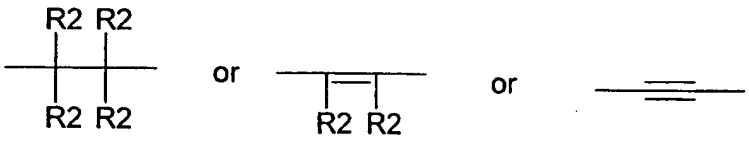
R1 is H or alkyl;

R2 is H or alkyl;

R3 is CH_2, O, or NOR4 wherein R4 is alkyl or substituted alkyl;

Q is CH or N,

A is



and n is 1-10.

14. The pharmaceutical composition of claim 13, wherein each linker X is independently selected from a structure of Table 1.

15. The pharmaceutical composition of claim 14, wherein *p* is an integer of from 2 to 4, and *q* is less than *p*.

16. A method of preparing a multibinding compound represented by formula I:

$$(L)_p(X)_q \qquad (I)$$

wherein each L is a ligand that may be the same or different at each occurrence;

X is a linker that may be the same or different at each occurrence;

p is an integer of from 2 to 10; and

q is an integer of from 1 to 20;

wherein each of said ligands comprises a ligand domain capable of binding to one of a RXR receptor or a PPARγ receptor, and where *q* is less than *p*,

(a) providing at least *p* equivalents of a ligand L or precursors thereof and at least *q* equivalents of linker or linkers X; and

(b) covalently attaching said ligands to said linkers to produce a multibinding compound; or

(b') covalently attaching said ligand precursors to said linkers and completing the synthesis of said ligands thereupon, thereby to produce a multibinding compound,

with the proviso that when one L is a ligand domain capable of binding to a RXR receptor, at least one other L must be a ligand domain capable of binding to a PPARγ receptor.

17. The method of claim 16, wherein *p* is an integer of from 2 to 4, and *q* is less than *p*.

18. A method for increasing insulin sensitivity in a mammal, which method comprises administering to a mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and one or more multibinding compounds represented by formula I,

$$(L)_p(X)_q \qquad (I)$$

and pharmaceutically acceptable salts thereof,

wherein

each L is a ligand that may be the same or different at each occurrence;

X is a linker that may be the same or different at each occurrence;

p is an integer of from 2 to 10; and

q is an integer of from 1 to 20;

wherein each of said ligands comprises a ligand domain capable of binding to one of a RXR receptor or a PPARγ receptor, and where q is less than p,

with the proviso that when one L is a ligand domain capable of binding to a RXR receptor, at least one other L must be a ligand domain capable of binding to a PPARγ receptor.

19. The method of claim 18, wherein p is an integer of from 2 to 4 and q is less than p.

20. A method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties.

21. A method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties.

22. The method according to Claim 20 or 21 wherein the preparation of the multimeric ligand compound library is achieved by either the sequential or concurrent combination of the two or more stoichiometric equivalents of the ligands identified in (a) with the linkers identified in (b).

23. The method according to Claim 22 wherein the multimeric ligand compounds comprising the multimeric ligand compound library are dimeric.

24. The method according to Claim 23 wherein the dimeric ligand compounds comprising the dimeric ligand compound library are heterodimeric.

25. The method according to Claim 24 wherein the heterodimeric ligand compound library is prepared by sequential addition of a first and second ligand.

26. The method according to Claim 20 or 21 wherein, prior to procedure (d), each member of the multimeric ligand compound library is isolated from the library.

27. The method according to Claim 26 wherein each member of the library is isolated by preparative liquid chromatography mass spectrometry (LCMS).

28. The method according to Claim 20 or Claim 21 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers.

29. The method according to Claim 28 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

30. The method according to Claim 29 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.

31. The method according to Claim 20 or 21 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.

32. The method according to Claim 31 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

33. The method according to Claim 20 or Claim 21 wherein the multimeric ligand compound library comprises homomeric ligand compounds.

34. The method according to Claim 20 or Claim 21 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

35. A library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

36. A library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

37. The library according to Claim 35 or Claim 36 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers.

38. The library according to Claim 37 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

39. The library according to Claim 38 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.

40. The library according to Claim 35 or 36 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.

41. The library according to Claim 40 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

42. The library according to Claim 36 or Claim 37 wherein the multimeric ligand compound library comprises homomeric ligand compounds.

43. The library according to Claim 35 or Claim 36 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

44. An iterative method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

(a) preparing a first collection or iteration of multimeric compounds which is prepared by contacting at least two stoichiometric equivalents of the ligand or mixture of ligands which target a receptor with a linker or mixture of linkers wherein said ligand or mixture of ligands comprises at least one reactive functionality and said linker or mixture of linkers comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand wherein said contacting is conducted under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands;

(b) assaying said first collection or iteration of multimeric compounds to assess which if any of said multimeric compounds possess multibinding properties;

(c) repeating the process of (a) and (b) above until at least one multimeric compound is found to possess multibinding properties;

(d) evaluating what molecular constraints imparted or are consistent with imparting multibinding properties to the multimeric compound or compounds found in the first iteration recited in (a)- (c) above;

(e) creating a second collection or iteration of multimeric compounds which elaborates upon the particular molecular constraints imparting multibinding properties to the multimeric compound or compounds found in said first iteration;

(f) evaluating what molecular constraints imparted or are consistent with imparting enhanced multibinding properties to the multimeric compound or compounds found in the second collection or iteration recited in (e) above;

(g) optionally repeating steps (e) and (f) to further elaborate upon said molecular constraints.

45. The method according to Claim 44 wherein steps (e) and (f) are repeated from 2-50 times.

46. The method according to Claim 44 wherein steps (e) and (f) are repeated from 5-50 times.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12669

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/1.11, 9.1, 178.1, ~~193.1; 435/7.1, 7.2; 436/501, 518; 514/365, 438, 469, 648, 706~~; 530/345, 389.1, 402, 807

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,587,046 A (GOODMAN et al) 06 May 1986 (06/05/86), see entire document, especially columns 1-7.	1-46
Y	WO 97/35195 A1 (THE SALK INSTITUTE FOR BIOLOGICAL STUDIES) 25 September 1997 (25/09/97), see page 3 lines 17-32, page 4 lines 1-18, page 5 lines 31-34, page 6 lines 1-10, page 7 lines 26-34, page 8 lines 1-5 and claims 13, 35 & 36.	1-46
Y	CHEN et al. Cooperative Formation of High-Order Oligiomers by Retinoid X Receptors: An Unexpected Mode of DNA Recognition. Proc. Natl. Acad. Sci. USA. January 1995. Vol. 92, No. 2, pages 422-426. See entire artcile, especially Abstract.	1, 2, 9-12, 16-19

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 07 OCTOBER 1999	Date of mailing of the international search report 29 OCT 1999
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12669

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LEHMANN et al. Peroxisome Proliferator-activated Receptors A and G are Activated by Indomethacin and Other Non-steroidal Anti-inflammatory Drugs. J. Biol. Chem. 07 February 1997. Vol. 272, No. 6, pages 3406-3410. See entire article.	1, 2, 9-12, 16-19
Y, P	COLLINS et al. N-(2-Benzoylphenyl)-L-Tyrosine PPAR-G Agonists. 2. Structure-Activity Relationships and Optimization of the Phenyl Alkyl Ether Moiety. J. Med. Chem. 03 December 1998. Vol. 41, pages 5037-5054. See entire article, especially Table 1.	1, 2, 9-12, 16-19
Y, P	US 5,814,647 A (URBAN et al) 29 September 1998 (25/09/98), see entire document, especially compounds in columns 3-10.	1-3, 9-19
Y, P	US 5,859,051 A (ADAMS et al) 12 January 1999 (12/01/99), see entire document, especially compounds in columns 3-10 and Example 6, column 22.	1, 2, 4, 5, 9-19
Y, P	US 5,847,008 A (DOEBBER et al) 08 December 1998 (08/12/98), see entire document, especially compounds in columns 3-6.	1, 2, 6, 9-19
Y, P	US 5,902,726 A (KLIEWER et al) 11 May 1999 (11/05/99), see entire document, especially compounds in columns 3-7.	1, 2, 7, 9-19
Y	US 4,929,635 A (COQUELET et al) 29 May 1990 (29/05/90), see entire document, especially Abstract.	1, 2, 8-19
X, P ---- Y, P	US 5,830,918 A (SPORTSMAN et al) 03 November 1998 (03/11/98), see entire document, espcially Abstract and columns 2-3.	1, 2, 9-12, 16-19 ---- 3-8, 13-15
X ---- Y	LIANG et al. Parallel Synthesis and Screening of a Solid Phase Carbohydrate Library. Science. 29 November 1996. Vol. 274, pages 1520-1522. See entire article.	36, 37, 43 ---- 20-35, 38-42, 44-46
X ---- Y	COLE et al. Discovery of Chiral CAtalysts through Ligand Diversity: Ti-Catalyzed Enantioselective Addition of TMSCN to meso Epoxides. Angew. Chem. Intl. Ed. Engl. 1996. Vol. 35, No. 15, apges 1668-1671. See pages 1669-1670, Figure 1 and Scheme 2.	35-38, 43 ---- 20-34, 39-42, 44-46
Y	DAVIS et al. Drug Leads from Combinatorial Phosphoidiester Libraries. J. Med. Chem. 27 October 1995. Vol. 38, No. 2, pages 4363-4366. See entire article.	20-46

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12669

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MENGER et al. Phosphatase Catalysis Developed via Combinatorial Organic Chemistry. J. Org. Chem. 1995. Vol. 60, pages 6666-6667. See entire article.	20-46
Y	SHUKER et al. Discovering High-Affinity Ligands for Proteins: SAR by NMR. Science. 29 November 1996. Vol. 274, pages 1531-1534. See entire article, especially Figure 1.	20-46

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12669

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/095, 31/135, 31/28, 31/44, 38/00, 39/00, 39/44, 39/395, 51/00; C07K 2/00, 4/00; G01N 33/53, 33/543, 33/566

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/1.11, 9.1, 178.1, 193.1; 435/7.1, 7.2; 436/501, 518; 514/365, 438, 469, 648, 706; 530/345, 389.1, 402, 807

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN (Registry, CAPLUS, SciSearch, MEDLINE)
Search terms: Structure search, PPAR, gamma, RXR, receptor, ligand, bind?, multibinding, polyvalent, multivalent, divalent, multimer, dimer, combinatorial

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-19, drawn to multibinding compounds capable of binding to a RXR or PPAR receptor, pharmaceutical compositions, method of preparation and method of increasing insulin sensitivity.
Group II, claim(s) 20-34, drawn to a method of identifying multimeric ligand compounds.
Group III, claim(s) 35-43, drawn to a library of multimeric ligand compounds.
Group IV, claim(s) 44-46, drawn to an iterative method for identifying multimeric ligand compounds possessing multibinding properties.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

Group I contains the following species:
Compounds labelled A-K and numbered II-IV.

The claims are deemed to correspond to the species listed above in the following manner:

Species A: 3
Species B: 4
Species C: 5
Species D: 6
Species E: 6
Species F: 7
Species G: 7
Species H: 7
Species I: 7
Species J: 7
Species K: 7
Species II: 8
Species III: 8
Species IV: 8

The following claims are generic: 1-2, 9-19.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12669

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group I does not share a special technical feature with Groups II-IV. The technical feature that links all of the claims of Group I is the multibinding compound capable of binding to a RXR or PPAR receptor. The feature that links the claims in Groups II-IV is the library of multimeric ligand compounds. Note that the requirement that these compounds be capable of binding to a RXR or PPAR receptor is not present in Groups II-IV. Furthermore, Groups II-IV lack unity because the libraries are known in the art.

For example, Cole et al (Angew. Chem. Int.Ed. Engl., 1996, Vol. 35, No. 15, pp. 1668-1671) teaches "diverse peptide-based structures" that can be collectively screened to search for chiral catalysts (see page 1669, 1st column). These ligands possess at least three sites for binding, as shown in structure 3 (2 hydroxy groups and the nitrogen). Figure 1 of Cole et al (page 1670) shows the variation of the ligand components. The middle amino acid component (AA2) is a linker, with the amino and acid ends comprising two functional groups having complementary reactivity to the other portions of the ligand. Cole et al shows using a library of linkers (choices for AA2 in Figure 1). The other portions are varied as shown in the figure (other amino acid segment and aldehyde segments a-m)and form covalent linkages to AA2 by reaction with the complementary functional groups (see Scheme 2, page 1669).

Additionally, Menger et al (J. Org. Chem., 1995, Vol. 60, pp. 6666-6667) teaches a multimeric ligand compound library comprising a single linker molecule. The linker is polyallylamine, which has a multitude of amino groups that are complementary to the library of ligands having a reactive carboxylic acid functionality. The library of ligands are covalently attached to the linker polymer, this is shown in Figure 1 (page 6666).

PCT Rule 13.2 states that unity of invention shall be fulfilled when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features". It further defines "special technical feature" as "those technical features that define a contribution which each of the claimed inventions, claimed as a whole, makes over the prior art". For example, unity of invention is fulfilled if:
(a) all alternatives have a common property; and
(b) (i) a common structure is present, i. e. a significant structural element is shared by all alternatives, or
(b) (ii) in cases where the common structure can not be the unifying criterion, all alternatives belong to a recognized class of compounds in the art to which the invention pertains. (MPEP Section 1850).

In the instant case, part (a) above is fulfilled because all claimed species of ligand have a common property. However, the compounds encompassed by the instant formulas do not all possess a common structure (no shared significant structural element). Further, all of the species do not belong to a recognized class of compounds in the art to which they pertain. For the forgoing reasons, election under these rules is proper and required.